

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022519Orig1s000

OTHER REVIEW(S)

505(b)(2) ASSESSMENT

Application Information		
NDA # 022519	NDA Supplement #: S-	Efficacy Supplement Type SE-
Proprietary Name: Duexis Established/Proper Name: ibuprofen and famotidine Dosage Form: Fixed-dose Combination Tablet Strengths: 800 mg ibuprofen / 26.6 mg famotidine		
Applicant: Horizon Pharma, Inc.		
Date of Receipt: March 23, 2010		
PDUFA Goal Date: January 23, 2011 PDUFA Goal Date (Major Amendment): April 23, 2011		Action Goal Date (if different):
Proposed Indication: Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen		

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 or by reliance on published literature. *(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 referenced product)	Information provided (e.g., pharmacokinetic data, or specific sections of labeling)
Motrin (ibuprofen) / NDA 017463	<p>Highlights:</p> <ul style="list-style-type: none"> Boxed Warning Contraindications Warnings and Precautions Drug Interactions Use in Specific Populations Patient Counseling Information <p>Full Prescribing Information:</p> <ul style="list-style-type: none"> Boxed Warning Section 1 Indications and Usage Section 4 Contraindications Section 5.2 Cardiovascular Effects Section 5.3 Gastrointestinal Effects Section 5.4 Renal Effects Section 5.5 Anaphylactoid Reactions Section 5.6 Skin Reactions Section 5.7 Pregnancy Section 5.8 Corticosteroid Treatment Section 5.9 Masking of Inflammation and Fever Section 5.10 Hepatic Effects Section 5.11 Hematological Effects Section 5.12 Pre-existing Asthma Section 5.13 Aseptic Meningitis Section 5.14 Laboratory Tests Section 6.1 Clinical Trials Experience Section 7 Drug Interactions <ul style="list-style-type: none"> Section 7.1 ACE-Inhibitors Section 7.2 Aspirin Section 7.3 Diuretics Section 7.4 Lithium Section 7.5 Methotrexate Section 7.6 Warfarin-Type Anticoagulants Section 8.1 Pregnancy Section 8.2 Labor and Delivery Section 8.3 Nursing Mothers Section 8.4 Pediatric Use Section 8.5 Geriatric Use Section 10 Overdosage Section 11 Description Section 12.1 Mechanism of Action

	Section 12.3 Pharmacokinetics Section 17 Patient Counseling Information
Pepcid (famotidine) / NDA 019462	Highlights: 1. Contraindications 2. Use in Specific Populations Full Prescribing Information: Section 4 Contraindications Section 5.1 Warnings and Precautions Section 5.4 Renal Effects Section 6.1 Clinical Trials Experience Section 7 Drug Interactions Section 8.1 Pregnancy Section 8.3 Nursing Mothers Section 8.5 Geriatric Use Section 10 Overdosage Section 11 Description Section 12.1 Mechanism of Action Section 12.3 Pharmacokinetics Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Section 13.2 Animal Toxicology and/or Pharmacology Section 17 Patient Counseling Information
Shibata, Yoshinaga, and Shiobara, 1983	Section 8.3 Nursing Mothers

*each source of information should be listed on separate rows

- 3) Reliance on information regarding another product (whether a previously approved product or from published literature) must be scientifically appropriate. An applicant needs to provide a scientific “bridge” to demonstrate the relationship of the referenced and proposed products. Describe how the applicant bridged the proposed product to the referenced product(s). (Example: BA/BE studies)

The sponsor conducted two studies to provide sufficient scientific evidence to demonstrate the relationship of the referenced product (Pepcid tablet, 40 mg) to the

famotidine component (26.6 mg) of proposed product. Study HZ-CA-001 is a single dose drug-drug interaction study that evaluated the pharmacokinetic profile of the referenced product, Pepcid, 40 mg tablet. Data from this single dose study were compared to data from Study HZ-CA-016, a food-drug interaction study that evaluated the commercial formulation of the proposed product (famotidine 26.6mg). The clinical pharmacologist estimated the multiple dose steady-state famotidine exposure (C_{max} and AUC) of the proposed product and demonstrated that the exposure was lower than that following a single dose of Pepcid, 40 mg. Therefore, these studies provide adequate scientific evidence bridging the proposed product to the listed drug, Pepcid tablets (famotidine).

The sponsor conducted a phase 1 bioequivalence study (HZ-CA-015) comparing the phase 3 formulation of HZT-501 to the Commercial ^{(b) (4)} formulation of HZT-501, the phase 3 formulation of HZT-501 to the listed drug Motrin (ibuprofen), and the Commercial ^{(b) (4)} formulation of HZT-501 to the listed drug Motrin (ibuprofen). The objective of the study was to demonstrate bioequivalence of famotidine in the phase 3 formulation of HZT-501 to the Commercial formulation of HZT-501, and the bioequivalence of ibuprofen in the phase 3 formulation of HZT-501 and the Commercial tablet formulation of HZT-501 to the listed drug Motrin (ibuprofen). Per the Clinical Pharmacology review discipline, the study is an acceptable bridge to the listed drug Motrin (ibuprofen).

Per the Nonclinical review discipline, the sponsor's use of *Shibata, Yoshinaga, and Shiobara, 1983*, to support claims made in Section 8.3 of the package insert is acceptable. Additionally, nonclinical bridging data for the famotidine component of the proposed product is not required because the safety of the proposed daily dose has been established previously. For the famotidine component of the proposed product the safety of the total daily dose (26.6x3 =79.8 mg) was established by comparison to safety data contained in NDA 19-462 (Pepcid; 80 mg daily dose).

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 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 referenced the 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/ANDA #(s). Please indicate if the applicant explicitly identified the product as being relied upon (see note below):

Name of Drug	NDA/ANDA #	Did applicant specify reliance on the product? (Y/N)
Motrin (ibuprofen)	NDA 017463	Yes (356h and Section 2.2 of eCTD (page 1))
Pepcid (famotidine)	NDA 019462	Yes (356h and Section 2.2 of eCTD (page 1))

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 monograph?

YES NO
If "YES", please list which drug(s).

Name of drug(s) described in a 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:

Motrin (ibuprofen) NDA 017463 was discontinued from marketing. Per the August 24, 2009, review by Igor Cerny, the product was not withdrawn from sale for reasons of safety and effectiveness.

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").

NDA 022519 provides for a new fixed-dose combination tablet of ibuprofen and famotidine.

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 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)).

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?

YES NO

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)?

YES NO

If “**YES**” and there are no additional pharmaceutical alternatives listed, proceed to question #12.

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

Pharmaceutical alternative(s):

PATENT CERTIFICATION/STATEMENTS

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

Listed drug/Patent number(s):

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 number(s):

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

Patent number(s):

Expiry date(s):

- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification). *If Paragraph IV certification was submitted, proceed to question #15.*
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the NDA holder/patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above). *If the applicant has a licensing agreement with the NDA holder/patent owner, proceed to question #15.*
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

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

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

- (a) Patent number(s):
- (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):

- (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/

JAGJIT S GREWAL
04/23/2011

DONNA J GRIEBEL
04/23/2011

SEALD LABELING: PI SIGN-OFF REVIEW

APPLICATION NUMBER	NDA 22-519 (b) (4)
APPLICANT	Horizon Pharma, Inc.
PRODUCT NAME	DUEXIS (ibuprofen/famotidine)
SUBMISSION DATE	March 23, 2010
PDUFA DATE	April 22, 2011 (clinical efficacy)
SEALD SIGN-OFF DATE	April 22, 2011
OND ASSOCIATE DIRECTOR FOR STUDY ENDPOINTS AND LABELING	Ann Marie Trentacosti for Laurie Burke

This memo confirms that all critical prescribing information (PI) deficiencies noted in the SEALD Labeling Review filed April 22, 2011, have been addressed in the final agreed-upon PI. SEALD has no objection to PI approval at this time.

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/s/

ANN M TRENTACOSTI
04/22/2011
Signing for Laurie Burke

SEALD LABELING REVIEW

This SEALD Labeling Review identifies major aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57 and related CDER labeling policies.

APPLICATION NUMBER	NDA 22-519 (b) (4)
APPLICANT	Horizon Pharma, Inc.
PRODUCT NAME	DUEXIS (ibuprofen/famotidine)
SUBMISSION DATE	March 23, 2010
PDUFA DATE	April 22, 2011 (clinical efficacy)
SEALD REVIEW DATE	April 22, 2011
SEALD LABELING REVIEWER	Jeanne Marie Delasko, RN, MS Label Initiatives Specialist

The following checked Selected Requirements for Prescribing Information items are outstanding labeling issues that must be corrected before the final draft labeling is approved.

Selected Requirements for Prescribing Information (SRPI)

This document is meant to be used as a checklist in order to identify critical issues during labeling development and review. For additional information concerning the content and format of the prescribing information, see regulatory requirements (21 CFR 201.56 and 201.57) and labeling guidances. When used in reviewing the PI, only identified deficiencies should be checked.

Highlights (HL)

- **General comments**

- HL must be in two-column format, with ½ inch margins on all sides and between columns, and in a minimum of 8-point font.
- HL is limited in length to one-half page. If it is longer than one-half page, a waiver has been granted or requested by the applicant in this submission.
- There is no redundancy of information. [JMDCComment: Since “Starting at 30 weeks gestation, DUEXIS should not be used by pregnant women as premature closure of the ductus arteriosus in the fetus may occur. (4)” is listed as a Contraindication in HL, do not repeat the same statement again (first bulleted item) under Use in Specific Populations heading in HL.]
- If a Boxed Warning is present, it must be limited to 20 lines. (Boxed Warning lines do not count against the one-half page requirement.)
- A horizontal line must separate the HL and Table of Contents (TOC).
- All headings must be presented in the center of a horizontal line, in UPPER-CASE letters and **bold** type.
- Each summarized statement must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contains more detailed information.
- Section headings are presented in the following order:

• Highlights Limitation Statement (required statement)
• Drug names, dosage form, route of administration, and controlled substance symbol, if applicable (required information)
• Initial U.S. Approval (required information)
• Boxed Warning (if applicable)
• Recent Major Changes (for a supplement)
• Indications and Usage (required information)
• Dosage and Administration (required information)
• Dosage Forms and Strengths (required information)
• Contraindications (required heading – if no contraindications are known, it must state “None”)
• Warnings and Precautions (required information)

• Adverse Reactions (required AR contact reporting statement)
• Drug Interactions (optional heading)
• Use in Specific Populations (optional heading)
• Patient Counseling Information Statement (required statement)
• Revision Date (required information)

- **Highlights Limitation Statement**
 - Must be placed at the beginning of HL, **bolded**, and read as follows: “**These highlights do not include all the information needed to use (insert name of drug product in UPPER CASE) safely and effectively. See full prescribing information for (insert name of drug product in UPPER CASE).**”
- **Product Title**
 - Must be **bolded** and note the proprietary and established drug names, followed by the dosage form, route of administration (ROA), and, if applicable, controlled substance symbol. [JMDCComment: **Include ROA. Should state; “. . . tablets, for oral use.”**]
- **Initial U.S. Approval**
 - The verbatim statement “Initial U.S. Approval” followed by the 4-digit year in which the FDA initially approved of the new molecular entity (NME), new biological product, or new combination of active ingredients, must be placed immediately beneath the product title line. If this is an NME, the year must correspond to the current approval action.
- **Boxed Warning**
 - All text in the boxed warning is **bolded**.
 - Summary of the warning must not exceed a length of 20 lines.
 - Requires a heading in UPPER-CASE, **bolded** letters containing the word “**WARNING**” and other words to identify the subject of the warning (e.g., “**WARNING: LIFE-THREATENING ADVERSE REACTIONS**”).
 - Must have the verbatim statement “*See full prescribing information for complete boxed warning.*” If the boxed warning in HL is identical to boxed warning in FPI, this statement is not necessary.
- **Recent Major Changes (RMC)**
 - Applies only to supplements and is limited to substantive changes in five sections: Boxed Warning, Indications and Usage, Dosage and Administration, Contraindications, and Warnings and Precautions.
 - The heading and, if appropriate, subheading of each section affected by the recent change must be listed with the date (MM/YYYY) of supplement approval. For example, “Dosage and Administration, Coronary Stenting (2.2) --- 2/2010.”
 - For each RMC listed, the corresponding new or modified text in the FPI must be marked with a vertical line (“margin mark”) on the left edge.
 - A changed section must be listed for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year.
 - Removal of a section or subsection should be noted. For example, “Dosage and Administration, Coronary Stenting (2.2) --- removal 2/2010.”

- **Indications and Usage**

- If a product belongs to an established pharmacologic class, the following statement is required in HL: [Drug/Biologic Product) is a (name of class) indicated for (indication(s)).” Identify the established pharmacologic class for the drug at:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162549.htm>.

- **Contraindications**

- This section must be included in HL and cannot be omitted. If there are no contraindications, state “None.”
- All contraindications listed in the FPI must also be listed in HL.
- List known hazards and not theoretical possibilities (i.e., hypersensitivity to the drug or any inactive ingredient). If the contraindication is not theoretical, describe the type and nature of the adverse reaction.
- For drugs with a pregnancy Category X, state “Pregnancy” and reference Contraindications section (4) in the FPI.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(a)(11) are included in HL. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided. Note the criteria used to determine their inclusion (e.g., incidence rate greater than X%).
- For drug products other than vaccines, the verbatim **bolded** statement, “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**” must be present. Only include toll-free numbers.

- **Patient Counseling Information Statement**

- Must include the verbatim statement: “**See 17 for Patient Counseling Information**” or if the product has FDA-approved patient labeling: “**See 17 for Patient Counseling Information and (insert either “FDA-approved patient labeling” or “Medication Guide”)**”.

- **Revision Date**

- A placeholder for the revision date, presented as “Revised: MM/YYYY or Month Year,” must appear at the end of HL. The revision date is the month/year of application or supplement approval. **[JMDCComment: Remember to update upon approval.]**

Contents: Table of Contents (TOC)

- The heading **FULL PRESCRIBING INFORMATION: CONTENTS** must appear at the beginning in UPPER CASE and **bold** type.
- The section headings and subheadings (including the title of boxed warning) in the TOC must match the headings and subheadings in the FPI.
- All section headings must be in **bold** type, and subsection headings must be indented and not bolded.
- When a section or subsection is omitted, the numbering does not change. For example, under Use in Specific Populations, if the subsection 8.2 (Labor and Delivery) is omitted, it must read:
 - 8.1 Pregnancy
 - 8.3 Nursing Mothers (not 8.2)
 - 8.4 Pediatric Use (not 8.3)
 - 8.5 Geriatric Use (not 8.4)
- If a section or subsection 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.”

Full Prescribing Information (FPI)

• General Format

- A horizontal line must separate the TOC and FPI.
- The heading **FULL PRESCRIBING INFORMATION** must appear at the beginning in UPPER CASE and **bold** type.
- The section and subsection headings must be named and numbered in accordance with 21 CFR 201.56(d)(1).

• Boxed Warning

- Must have a heading, in UPPER CASE, **bold** type, containing the word “**WARNING**” and other words to identify the subject of the warning. Use **bold** type and lower-case letters for the text.
- Must include a brief, concise summary of critical information and cross-reference to detailed discussion in other sections (e.g., Contraindications, Warnings and Precautions).

• Contraindications

- For Pregnancy Category X drugs, list pregnancy as a contraindication.

- **Adverse Reactions**

- Only “adverse reactions” as defined in 21 CFR 201.57(c)(7) should be included in labeling. Other terms, such as “adverse events” or “treatment-emergent adverse events,” should be avoided.

- For the “Clinical Trials Experience” subsection, the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

- For the “Postmarketing Experience” subsection, the listing of post-approval adverse reactions must be separate from the listing of adverse reactions identified in clinical trials. Include the following verbatim statement or appropriate modification:

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

- **Use in Specific Populations**

- Subsections 8.4 Pediatric Use and 8.5 Geriatric Use are required and cannot be omitted.

- **Patient Counseling Information**

- This section is required and cannot be omitted.

- Must reference any FDA-approved patient labeling, including the type of patient labeling. The statement “See FDA-approved patient labeling (insert type of patient labeling).” should appear at the beginning of Section 17 for prominence. For example:

- “See FDA-approved patient labeling (Medication Guide)”
- “See FDA-approved patient labeling (Medication Guide and Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information)”
- “See FDA-approved patient labeling (Instructions for Use)”
- “See FDA-approved patient labeling (Patient Information and Instructions for Use)”

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/s/

JEANNE M DELASKO
04/22/2011

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>July 2013</u>
	Study/Trial Completion:	<u>July 2015</u>
	Final Report Submission:	<u>March 2016</u>
	Other:	_____

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

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

Pediatric deferral for children was granted at PeRC on 08DEC2010 because adult studies are ready for approval.

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

The drug has not been studied in the pediatric population.

(b) (4)
The sponsor must attempt to develop an age appropriate formulation or provide adequate justification that such a formulation is not feasible.

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

If not a PMR, skip to 4.

Which regulation?

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Development of age-appropriate formulation for pediatric use.
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as CT, C_{max}, T_{max}, AUC, T_{1/2}, clearance, and Vd_{ss}, as applicable.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	July 2016
	Study/Trial Completion:	December 2016
	Final Report Submission:	March 2017
	Other:	_____

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

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

Pediatric deferral for children was granted at PeRC on 08DEC2010 because adult studies are ready for approval.

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

The drug has not been studied in the pediatric population.

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

If not a PMR, skip to 4.

Which regulation?

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as CT, Cmax, Tmax, AUC, T1/2, clearance, and Vdss, as applicable.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

Attachment B: Sample PMR/PMC Development Template

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

PMR/PMC Description: A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	October 2011
	Study/Trial Completion:	October 2013
	Final Report Submission:	May 2014
	Other:	_____

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

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

Pediatric deferral for children 1 year, 11 months to 16 years, 11 months of age was granted at PeRC on 08DEC2010 because adult studies are ready for approval. This study will evaluate the product in patients 10 to 16 years 11 months, as this population can safely take the formulation already available. Patients younger than 10 years will be studied using an age appropriate formulation as part of a separate post-marketing requirement.

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

The drug has not been studied in the pediatric population.

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

If not a PMR, skip to 4.

Which regulation?

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

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

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

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

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?
Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

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

A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 16 years, 11 months.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

- Does the study/clinical trial meet criteria for PMRs or PMCs?
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-

PMR/PMC Development Coordinator:

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(signature line for BLAs)

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

PMR/PMC Description: A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 9 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 9 years, 11 months.

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>January 2016</u>
	Study/Trial Completion:	<u>January 2018</u>
	Final Report Submission:	<u>July 2018</u>
	Other:	_____

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

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

Pediatric deferral for children 1 year, 11 months to 16 years, 11 months of age was granted at PeRC on 08DEC2010 because adult studies are ready for approval. This study will evaluate the product in patients 2 to 9 years, 11 months of age after the applicant has developed an age appropriate formulation. Patients 10 years of age and older will be studied using the approved product as part of a separate post-marketing requirement.

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

The drug has not been studied in the pediatric population.

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

If not a PMR, skip to 4.

Which regulation?

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

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

A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 9 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 9 years, 11 months.

Required

- Observational pharmacoepidemiologic study
 Registry studies
 Primary safety study or clinical trial
 Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 Thorough Q-T clinical trial
 Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

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

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

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

PMR/PMC Development Coordinator:

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

(signature line for BLAs)

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

/s/

JAGJIT S GREWAL
04/22/2011

LYNNE P YAO
04/22/2011

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 4/8/11

TO: Todd Phillips, PharmD
Project Manager; Division of Gastroenterology Products

FROM: Khairy Malek, M.D., Ph.D
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-519

APPLICANT: Horizon Pharma, Inc.

DRUG: (b) (4) (ibuprofen/fomatidine) Tablets

NME: NO

THERAPEUTIC CLASSIFICATION: Standard

INDICATIONS: 1. Risk reduction of ibuprofen associated upper gastrointestinal
Ulcers in patients who require use of ibuprofen

CONSULTATION REQUEST DATE: June 09, 2010, December 10, 2010

Inspection Summary Goal Date: February 18, 2011

PDUFA DATE: April 22, 2011 (PDUFA Extension Date)

1. BACKGROUND:

Horizon Pharma, Inc. submitted this New Drug Application for the use of the combination product (b) (4) (ibuprofen and famotidine) for the risk reduction of ibuprofen associated upper gastrointestinal ulcers in patients who require the use of ibuprofen. The pharmacologic actions of ibuprofen include anti-inflammatory activity, analgesic and antipyretic activities and reduction of platelet aggregation. Ibuprofen causes gastrointestinal bleeding and the development of gastric and duodenal ulcers. This ulceration results from impairment of mucosal integrity secondary to inhibition of prostaglandin synthesis. In the presence of reduced mucosal integrity, gastric acid is more likely to cause of irritation and ulceration.

Famotidine is a specific long-acting H₂ receptor antagonist. This inhibition of the action of histamine at the H₂ receptors on parietal cells results in inhibition of gastric acid secretion. Many clinical studies have demonstrated reduced gastrointestinal toxicity when ibuprofen and famotidine are administered together. Each pill of the study drug (HZE-501) contains 800 mg ibuprofen and 26.6 mg of famotidine.

Two studies were conducted in support of this NDA:

Protocol HZ-CA-301, entitled “A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZE-501 in Subjects Requiring NSAID Treatment”.

Protocol HZ-CA-303, entitled “A Randomized, Double-Blind, Phase 3 Study of the Efficacy and Safety of HZE-501 in Subjects Requiring NSAID Treatment”

Five clinical sites and the sponsor were inspected in support of this application. The review division had initially requested 3 clinical site inspections in June 2010: Drs. Serbousek, Abraham, and Mancha. Drs. Serbousek’s and Mancha’s sites were selected for inspection due to a relatively high enrollment of subjects. Dr. Abraham’s site was selected for inspection because this site had a disproportionately higher rate of ulcers in the placebo group compared to other sites. An additional request for clinical site inspections was submitted to DSI in December 2010 which included inspection requests for the clinical sites of Drs. Kumar and Riff. These additional sites were selected for inspection due to relatively higher enrollments as well as early termination with or without ulcer. Additionally, a previous inspection of Dr. Riff for another application had raised some concerns with respect to e-Diary related data as well enrollment of ineligible subjects, and as this application also included data collected by Dr. Riff, Dr. Riff’s site was selected to specifically evaluate the conduct of the pivotal study in support of this application. An inspection of the sponsor was conducted to evaluate execution of sponsor/monitoring responsibilities after significant issues were noted during the inspection of Dr. Mancha.

II. RESULTS (by Site):

Name of CI	Protocol #, Site # and # of Subjects	Inspection Date	Final Classification
LeAnn Serbousek, M.D. Sooner Clinical Research 5929 North May Ave, Suite 401 Oklahoma City, OK 73112 Tel: 405-843-9528	HZ-CA-301 Site # 144 38 Subjects	08/02/2010- 08/06/2010	NAI
William Abraham, M.D. Radiant Research, Inc. 7042 E. Broadway Boulevard Tucson, AZ 85710 Tel: 520-885-6793	HZ-CA-301 Site # 180 22 Subjects	09/13/2010- 09/14/2010	Pending Preliminary: NAI
Vaughn Mancha, M.D. Montgomery Surgical Center 855 East South Blvd Montgomery, AL 36116 Tel: 334-264-6054	HZ-CA-303 Site # 389 167 Subjects	09/07/2010- 09/23/2010	OAI: Warning Letter
Vrijendra Kumar, M.D. Advanced Biomedical Research of America 8420 South Eastern Ave, Suite 102 Las Vegas, NV 89123 Tel:	HZ-CA-303 Site # 340 35 Subjects	01/26/2011- 02/02/2011	Pending Preliminary: VAI
Dennis Riff, M.D. Advanced Clinical Research Institute 1211 W. La Palma Ave, Suite 602, 306, 303-Anaheim CA 92801 Tel:	HZ-CA-303 Site # 363 76 Subjects	01/26/2011- 02/14/2011	Pending Preliminary: VAI
Horizon Pharma, Inc. 1033 Skokie Boulevard, Suite 355 Northbrook, IL 60062 Tel: 224-383-3009	HZ-CA-301 HZ-CA-303	11/09/2010- 11/23/2010	Pending Preliminary: VAI

Key to Classifications

NAI No deviation from regulations.

VAI Deviation(s) from regulations.

OAI Significant deviations from regulations. Data unreliable.

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

1. **LeAnn Serbousek: Site # 144**

- a. What was inspected: The protocol investigated at this site was Protocol 301. At this site 83 subjects were screened and 38 subjects were randomized into the study and 24 subjects completed the study.

Thirty eight of the randomized subject's files were reviewed for completeness and accuracy. During the inspection source documents were compared against CRFs and NDA line listings. Documents reviewed in the audit included, signed informed consent forms, study eligibility (inclusion/exclusion criteria), patients' diaries, laboratory testing and randomization procedures. There was no limitation to the inspection.

- b. General observations/commentary: The study appears to have been conducted adequately at this site. The inspection revealed no violations of the federal regulations and a Form FDA 483 was not issued.
- c. Assessment of data integrity: The data from this site can be used in support of the NDA

2. **William Abraham, M.D.-Site # 180**

- a. What was inspected: At this site 34 subjects were screened, 22 were randomized and 15 completed the study. The field investigator reviewed the records of 15 subjects. This included informed consents, laboratory reports, primary efficacy database, adverse events, inclusion/exclusion criteria, and source documents. There was no limitation to the inspection.
- b. General observations/commentary: The Investigator found no deficiencies or violations to Federal regulations.
- c. Assessment of data integrity: The data from this site can be used in support of the NDA.

3. **Vaughn Mancha, M.D. - Site # 389**

- a. What was inspected: At this site 167 subjects were randomized and 103 completed the study. The field investigator reviewed the study records of 53 subjects including the Informed Consent Documents, inclusion/exclusion criteria, CRFs and source documents. This CI was not allowed by the monitor to proceed with Protocol 301 investigation due to the many violations observed. There was no limitation to the inspection.
- b. General Observations/commentary: **[This section completed by Branch Chief]**. The inspection documented that the study was not conducted adequately at this site. There were several issues noted with respect to failure to adhere to the protocol as well as maintenance of accurate records. The inspection documented that the majority of the deviations noted were due to lack of

adequate PI oversight of the study as well as hiring of inexperienced study staff. Due to number of deviations noted during the course of the study, the IRB had placed the site on temporary recruitment hold for all studies conducted by Dr. Mancha.

Further, Dr. Mancha reported that he had noticed the study coordinator documenting on source records that she had conducted *H. pylori* tests; however, the testing supplies were not used. He reported this suspected study misconduct immediately to the sponsor/monitor. Apparently 17 subjects were evaluated by this site coordinator before this issue was identified, after which, the study coordinator resigned. Following the identification of this issue, all records in which this study coordinator was involved were heavily scrutinized, and it was noted that there appeared to be at least one forged signature (apparently by the study coordinator) for a physical exam apparently conducted by the subinvestigator; this subinvestigator had denied signing this particular source document.

Examples of protocol deviations and inaccurate records follow.

i. The protocol violations included:

- The protocol specified that subjects who had used a nonsteroidal anti-inflammatory drug (NSAID) within the 30 days prior to study entry were ineligible for enrollment into the study. FDA's inspection documented that 8 subjects (389058, 389069, 389080, 389090, 389143, 389218, 389040 and 389111) had used an NSAID within the 30 days prior to study entry but were enrolled into the study.
- The protocol specified that subjects who used an acid suppressant agent within 14 days prior to study entry were ineligible for enrollment into the study. FDA's inspection documented that 8 subjects (389086, 389094, 389173, 389234, 389085, 389092, 389142, and 389247) had used an acid suppressant agent within 14 days prior to study entry, yet were enrolled into the study.
- The protocol specified that at the screening visit, blood samples were to be collected from study subjects for on-site testing for serum *H. pylori*. The protocol further specified that subjects with a documented current *H. pylori* infection were ineligible for enrollment into the study. FDA inspection documented that at least 5 subjects (389127, 389135, 389129, 389137, and 389142) were enrolled into the study without documentation of a current negative *H. pylori* test at the screening visit.
- The protocol specified that all subjects on anticoagulant therapy undergo International Normalized Ratio (INR) testing at the screening visit. This was not completed for at least 2 subjects (389017 and 389085)
- For at least two subjects (389162 and 389210) protocol specified study visits were not being scheduled per protocol requirements
- The protocol required that serum pregnancy tests be conducted at screening; however, this was not done for at least two subjects (389075 and 389211).

- At least 3 subjects (389013, 389041, and 389091) were dispensed incorrect test article kits that had been assigned for another subject as per the randomization assignment
 - An SAE of acute renal failure (based on creatinine value of 3.2 mg/dL) in Subject 389204 was not reported promptly to the sponsor or the IRB
 - For at least two subjects (389204 and 389602), there was a significant delay in the CI's review of the laboratory results
- ii. Inaccurate records included:
- At least 1 subject (389137) was enrolled without adequate documentation of a screening physical examination. This subject was screened by the study coordinator suspected of misconduct/fraud as described earlier in this section
 - For Subject 389230, the source physical exam was not documented as signed by the PI until approximately 4 months after the exam had taken place
 - Records are discrepant with respect to which subject had an out of window visit for Week 24, Subject 389198 or 389168

The following is excerpted from Dr. Dan-My Chu's DSI GCP-1 "Reviewer's Note to the Review Division" section of the Warning Letter sent to Dr. Mancha based on her critical review of the EIR as well as review of the exhibits:

In addition to the findings made during the FDA inspection, additional GCP deviations were noted including but not limited to redispensing of study drug to 33 subjects at week 8 and/or 16 in violation of the protocol, allowing multiple subjects to continue on study at week 4 without having assessed compliance with dosing, numerous out of window visits, and a subject continuing to take study drug after a gastric ulcer was discovered. These additional GCP deviations were identified subsequent to the review of information and protocol deviations sent to the IRB, multiple memos to files found at the site, and/or information sent to the CRO,

(b) (4)

Branch Chief Notes: Overall, the study does not appear to have been conducted adequately at this site. The most significant issues are

- 1) Study Coordinator Misconduct: identification that the study coordinator may have falsified records, potentially for 17 subjects, is concerning, although it is difficult to specifically document what/if anything other than one signature was falsified; this finding underscores the lack of CI oversight in the conduct of this study and is concerning for data reliability
- 2) Enrollment of ineligible subjects: 8 subjects of 53 subject records reviewed (15%) documented enrollment of subjects that were ineligible for study entry based on use of NSAID and an additional 8 subjects of 53 subject records reviewed (15%) were ineligible based on use of acid suppressant therapy, which is significant as these have the potential to confound the results for this combination drug product (NSAID with acid suppressant therapy) in the evaluation of safety and efficacy and therefore likely to impact data reliability.

- 3) Several other protocol violations were noted, which in itself as isolated incidents are unlikely to impact data reliability; however, are quite numerous when taken together, and again display the lack of CI oversight for the conduct of the study, and raise concerns as to data reliability
- 4) Additionally, numerous other violations were identified based on review of information for protocol deviations sent to the IRB, multiple memos to files found at the site, and/or information sent to the CRO.

Given that 100% of records were not inspected, and noting the numerous violations documented at the site in the records that were evaluated, as well as suggestion of study misconduct by the study coordinator, the confidence in the collected data is undermined and the reliability of the data is in question.

- c. Assessment of data integrity: Significant issues were either identified during the inspection and/or identified during the review of collected documents during the inspection, which undermine the confidence in the reliability of the data. The data from this site are unreliable, and can not be used in support of the NDA.

4. Horizon Pharma, Inc.

1033 Skokie Blvd, Suite 355, Northbrook, IL 60062

- a. What was inspected:

The Sponsor contracted the monitoring of all sites to a CRA (b) (4). Records reviewed during the inspection included: pre-study visits, site visit reports for all sites reviewed, site initiation visits, SOPs from (b) (4), monitoring reports, IRB approvals and correspondence, sponsor and CI correspondences, eCRFs, test article accountability logs, protocol deviations, AE reporting, and ICs.

Inspection covered the following protocols/CIs

Protocol 301:

LeAnn Serbousek, site 144

William Abraham, site 180

Suresh Gupta, site 166

Douglas Young, site 123

Protocol 303

Vaughn Mancha site 389

Paula Lane site 341

(b) (4) was responsible for IVRS randomization.

According to the contract between (b) (4) and Horizon, monitoring frequency to occur within the first 4 weeks of the first patient enrolled and subsequently on average approximately every 12 weeks with variations based on site performance (enrollment rate) and data quality. The plan also required monitors to perform 100% source document verification of all CRFs. The IMV (Interim monitoring visits) SOP states,

that at every visit, the monitor was to ensure review of records of all subjects screened since the last visit; ensure that the subjects have signed the ICD; verify inclusion/exclusion criteria; review any SAEs that occurred since the last visit and ensure that they were reported; ensure that protocol criteria were met and protocol violations were reported; ensure adequate study conduct by study site personnel and to report any non-compliance to the Lead CRA.

Field Investigator reviewed monitoring records from 6 sites. Those who participated in Protocol 301 were: Serbousek, Abraham, Gupta, and Young. Drs Mancha and Lane participated in Protocol 303. Enrollment at one site, Site # 166 (Dr. Gupta) was halted due to CI was non-compliance, demonstrating that adequate action was taken by the monitors at this site .

b. General Observations/Commentary:

The inspection revealed that monitoring appeared adequate in general at all sites, with the exception at Site 389 (Dr. Mancha). The CRA did not appear to secure prompt compliance at Site 389 and did follow SOP for reporting scientific misconduct. The frequency and resources dedicated to monitoring this site appeared inadequate due to the high enrollment at this site. At site 389 the first monitoring visit was 4 weeks after enrollment of first subject. IMVs 2-5 occurred every 43 days but it appears that the CRA was unable to review all applicable activities as required by SOP. At IMV # 5, there were 300 outstanding queries at the site. The frequency of the visits occurred every 14 days after IMV 5. Noted issues were:

- 29 subjects were re-dispensed study drug
- Drug accountability was reported in IMV #4 as “no issues” while there were issues from previous visit
- 15 study drug units were unaccounted for.
- The IMV #1 indicated that 39 subjects were screened and 12 randomized. The monitor spent one day and reviewed CRFs for 1 subject.
- As of IMV # 5, there were 300 outstanding queries; 72 subjects remained outstanding for source data verification and CRFs due to time restraints

Review of the files noted a data management defect with the electronic data management system related to source document verification flags and CI signature status. Data management obtained approval from each site to make changes as necessary since sites could no longer log into database due to the data lock. The Sponsor did not appear to make any corrections to the CRFs, however due to a defect in the electronic data capture system, some clarifications were made after the database was locked with the acknowledgements of the CIs.

All sites were audited by (b) (4) and Horizon. There were no under reporting of AEs. Data listings submitted to the FDA for 35 subjects, 19 from protocol 301 and 16 from 303 were reviewed and compared with eCRFs. No discrepancies were noted.

- c. **Assessment of Data Integrity:** Apart from the lacking of adequate monitoring at Dr. Mancha site, the sponsor's procedures were adequate and the data are considered acceptable. The inspection did not raise concerns for systemic issues with respect to monitoring and sponsor oversight of the pivotal studies, and it appears that the findings at Dr. Mancha's are isolated. With the exception of the data from Dr. Mancha's site, the data are considered reliable.

After the review division was informed of the unacceptability of the data from Dr. Mancha's site, the Division requested inspection of 2 additional CI sites as per below:

5. Vrijendra Kumar, M.D. - Site 340

- a. **What was inspected:** The protocol investigated at this site was # 303. At this site, 35 subjects were randomized and 14 subjects completed the study. The field investigator compared the data in the eCRFs to the data in the laboratory reports, progress reports, individual records and data provided in the assignment. There was no limitation to the inspection.
- b. **General Observations/Commentary:** During the inspection, regulatory violations were observed with respect to protocol violations and inaccurate records.
- i. **The protocol violations** were:
- Subject # 37 was admitted although the subject had 5 non-bleeding erosions at screening
 - Female Subject #54 was admitted without a pregnancy test performed
 - Subject # 79 took naproxen 500 mg for four days during the study
 - Subject 86 used a diclofenac patch for 3 days during treatment.
- ii. **Inaccurate records included:**
- Subjects # 44, 53, 55 and 78 had adverse reactions (cough, stomach ache, diarrhea, nausea, colitis and dry mouth) which were recorded as "not resolved" in the source documents and as "resolved" in the eCRFs
 - Subject # 86 had an ear infection recorded in the source documents but not submitted in the eCRF.
- c. **Assessment of Data Integrity:** Although regulatory violations were noted, these violations are not likely to affect the validity of the data as they are considered isolated in nature, and the data generated at this site can be used in support of the NDA.

6. Dennis Riff, M.D. Site # 363

- a. **What was inspected:** At this site, 76 subjects were admitted and 60 subjects completed the study. The protocol investigated at this site was Protocol # 303. The field investigator reviewed the records of 52 subjects. The review included: CRFs, inclusion/exclusion criteria, laboratory reports, test article accountability, adverse reactions and data listings. The monitor provided feedback needed advice. There was

no limitation to the inspection.

- b. General Observation/Commentary: The field investigator observed some violations which were: protocol violations, failure to prepare and maintain accurate records, and inaccurate drug accountability records.
- j. The protocol violations included:
- screening macro urine analysis were not done for 5 subjects # 024, 036, 054, 055 and 121
 - Pregnancy screening tests were not done for 2 female subjects, # 092 and 106
 - Subject #023 was dispensed the study drug before the EGD procedure was conducted.
- ii. Inaccurate records included:
- Subject #126 concomitant medications records show Aciphex as ongoing although it was discontinued
 - Subject 021 records were missing at the time of the FDA inspection
 - Subject 078 had a history of glaucoma but it was not documented on the General and Surgical History or the CRF. The same subject used medical marijuana and was not entered on the concomitant medication record.
- iii. Inaccurate drug disposition records included:
- Subject # 050 was dispensed the wrong study drug kit at randomization
 - Subject #005 study drug Kit #51048 was not documented on the subject accountability log, but was documented on the return supplies form. This kit # did not exist for the study; and Subject # 100 took the wrong kit number and mistakenly took double the instructed dose.
- c. Assessment of Data Integrity: Regulatory violations were noted with respect to protocol violations, inaccurate records, as well as inaccurate drug accountability records as described above. Based on the findings above, DSI recommends exclusion of 4 subjects from the Statistical analysis: Subject # 050 who was dispensed the wrong drug; Subject# 005 whose study kit number was not found; Subject 021 because the subject's records were not found at the time of the inspection and Subject # 100 who was dispensed the wrong kit and took double the specified dose.

Apart from these 4 subjects, the rest of the data are reliable and can be used in support of the NDA, as the rest of the noted violations appear isolated in nature and/or unlikely to significantly impact data reliability.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Five clinical sites and the sponsor were inspected in support of the application. The data from 4 out of the 5 Sites are considered reliable: Drs. Serbousek, #144; Abraham Site # 180; Kumar, Site #340; and Riff, Site 363. This also applies to Inspection of the Sponsor.

Regarding Dr. Riff's site, it is recommended that the 4 subjects mentioned above, # 005, 021, 050 and 100, be excluded from the Statistical Analysis; otherwise, the other data are considered reliable. Due to significant concerns regarding data reliability at Dr. Mancha's site, the data from Dr. Mancha's site are considered unreliable in support of the indication. Overall, the data collected in support of this application are considered reliable with the exception of the data from Dr. Mancha's site.

{See appended electronic signature page}

Khairy Malek, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

TEJASHRI S PUROHIT-SHETH
04/08/2011

MEMORANDUM

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

DATE: March 30, 2011

TO: Donna Griebel, M.D.
Director, Division of Gastroenterology Products
(HFD-180)

FROM: Gopa Biswas, Ph.D.
GLP and Bioequivalence Branch
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 3/30/2011*
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of (b) (4) response dated 1/27/11: Addendum
to review of EIR Covering NDA 22-519 (b) (4) Tablets,
Ibuprofen 800 mg/Famotidine 26.6 mg sponsored by
Horizon Pharma, Inc.

At the request of the Division of Gastroenterology Products, the Division of Scientific Investigations (DSI) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: HZ-CA-0-15

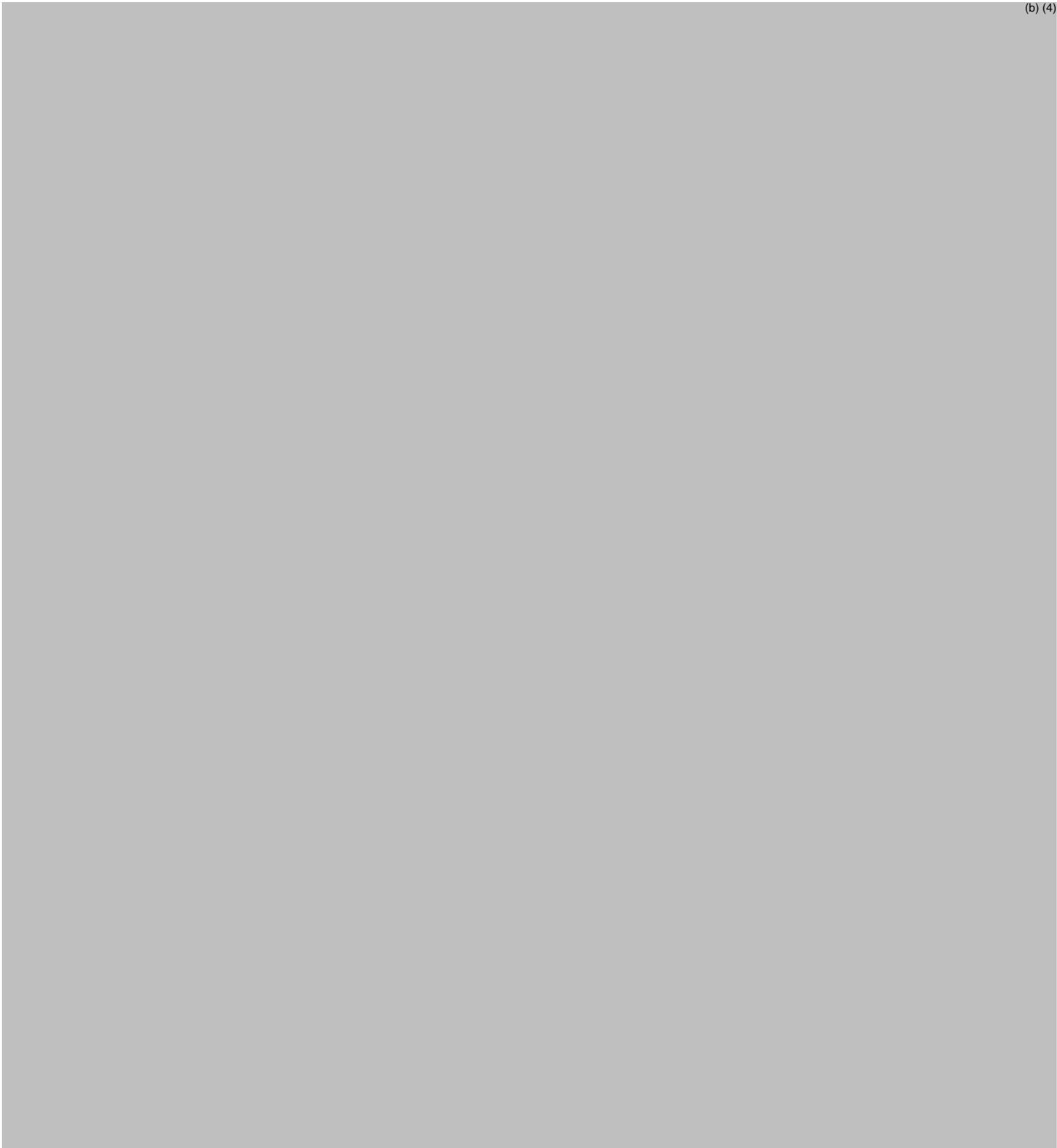
Study Title: "A Randomized, Three-Period Crossover, Oral, Single-Dose, Open-Label Study to Determine the Bioequivalence of Famotidine and Ibuprofen in the Phase 3 and (b) (4) Formulations of HZT 501, and to Determine the Bioequivalence of Ibuprofen in the Phase 3 and (b) (4) Formulations of HZT-501 to an Equivalent Dose of Commercially Available Ibuprofen, in Fasted, Healthy, Adult Subjects"

DSI's memo dated 2/24/2011 evaluated the Form 483 items resulting from the inspections at clinical site (Cetero Research, St. Charle, MO. 11/22-11/24/2011) and the analytical site ((b) (4) 1/4-1/7/2011), and Cetero's response received on 1/25/2011. DSI received a response from

(b) (4) dated 1/27/2011 on 1/31/2011 (Attachment 1). The response was not available to the reviewer at the writing of the initial review. This addendum will only cover DSI's evaluation of (b) (4) response as follows:

(b) (4)

(b) (4)



Conclusion:



Page 4 - NDA 22-519 Tablets, Ibuprofen 800 mg and Famotidine
26.6 mg

DSI evaluated and accepts (b) (4) written responses to 483
items 1, 3 and 4 to 7 as adequate. DSI's conclusions remain
same as in memo submitted on 2/24/2011 and recommends that the
analytical portion can be accepted for review.

After you have reviewed this transmittal memo, please append it
to the original NDA submission.



Gopa Biswas Ph.D.

Final Classifications:

VAI-Cetero Research-St. Charles, MO

VAI- (b) (4)

cc:

DSI/Ball/Haidar/Yau/Biswas/Dejernett/Viswanathan/CF
HFD-180/Phillips, Todd
OND/DCP/DGP/Griebel, Donna
HFR-SW450/Bous, Sherry
HFR-PA1530/Shrifter, Jeffrey
Draft: GB 3/22/2011
Edit: MKY 3/30/2011
DSI: 6113; O:\BE\eircover\22519hor.ibu.fam.addendum.doc
FACTS: 1202647

EMAIL:

CDER DSI PM TRACK

ATTACHMENT 1

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/s/

GOPA BISWAS
03/30/2011

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

PATIENT LABELING REVIEW

Date: March 21, 2011

To: Donna Griebel, MD, Director
Division of Gastroenterology Products (DGP)

Through: LaShawn Griffiths, RN, MSHS-PH, BSN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management (DRISK)
Barbara Fuller, RN, MSN, CWOCN
Acting Team Leader, Patient Labeling Reviewer
Division of Risk Management

From: Latonia M. Ford, RN, BSN, MBA
Patient Labeling Reviewer
Division of Risk Management

Subject: DRISK Review of Patient Labeling (Medication Guide)

Drug Name(s): DUEXIS (ibuprofen and famotidine)

Dosage Form and Route: tablets

Application Type/Number: NDA 22-519

Applicant/sponsor: Horizon Therapeutics, Inc

OSE RCM #: 2010-1014

1 INTRODUCTION

This review is written in response to a request by the Division of Gastroenterology Products (DGP) for the Division of Risk Management (DRISK) to review the Applicant's proposed Medication Guide (MG) for Duexis (ibuprofen and famotidine) tablets.

On March 23, 2010, Horizon Therapeutics submitted an original New Drug Application (NDA), 22-519 for Duexis (ibuprofen and famotidine) tablets for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal (GI) ulcers in patients who require use of ibuprofen.

2 MATERIAL REVIEWED

- Draft Duexis (ibuprofen and famotidine) tablets, Medication Guide (MG) received on March 23, 2010, and revised by Review Division throughout the current review cycle, and received by DRISK on March 10, 2011.
- Draft Duexis (ibuprofen and famotidine) tablets, Prescribing Information (PI) received on March 23, 2010, and revised by Review Division throughout the current review cycle, and received by DRISK on March 10, 2011.

3 RESULTS OF REVIEW

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

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

In our review of the MG, we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.24
- ensured that the Duexis MG is consistent with the currently approved NSAID MG template

- ensured that Duexis MG is consistent with the currently approved Vimovo where applicable

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DRISK on the correspondence.
- Our annotated versions of the MG are appended to this memo. Consult DRISK regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

LATONIA M FORD
03/22/2011

LASHAWN M GRIFFITHS
03/23/2011

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications**

*****Pre-decisional Agency Information*****

Memorandum

Date: 03/22/11

To: Jagjit Grewal, Regulatory Project Manager
Division of Gastroenterology Products (DGP)

From: Roberta Szydlo, Regulatory Review Officer
Kendra Jones, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

CC: Lisa Hubbard, Professional Group Leader
Shefali Doshi, DTC Group Leader
Kathleen Klemm, Regulatory Review Officer
Olga Salis, Regulatory Health Project Manager
Michael Wade, Regulatory Health Project Manager
(DDMAC)

Subject: NDA 022519
DDMAC labeling comments for DUEXIS™ (ibuprofen and famotidine) tablets

In response to DGP's May 10, 2010, consult request, DDMAC has reviewed the draft labeling (PI, Carton/Container Labeling, and Medication Guide) for DUEXIS™ (ibuprofen and famotidine) tablets.

DDMAC's comments on the proposed PI and Medication Guide are based on the proposed draft marked-up labeling titled, "NDA 22519draft PI 09JUL2010.doc," that was modified in the e-room on March 11, 2011 at 2:28pm.

DDMAC's comments on the PI and Medication Guide are provided directly in the marked-up document attached (see below). Please note that we have hidden the tracked changes and other reviewers' comments so that our comments are easier to read.

DDMAC has reviewed the proposed Carton/Container Labeling located in the EDR at: <\\cdsesub5\EVSPROD\NDA022519\0003\m1\us\draft-carton-container-labels.pdf>.

We offer the following comments on the proposed container label:

- We recommend that the proposed container label be revised to be consistent with CFR 201.10 (g)(2). Specifically, we recommend that the size of the established name be revised to be at least half as large as the proprietary name. We also recommend that the established name be presented with a prominence that is consistent with the presentation of the proprietary name in terms of type and font.

Thank you for the opportunity to comment on these proposed materials.

If you have any questions regarding the PI or container label, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov. If you have any questions regarding the Medication Guide, please contact Kendra Jones at (301) 796-3917 or kendra.jones@fda.hhs.gov.

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/s/

KENDRA Y JONES
03/22/2011

MEMORANDUM

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

DATE: February 22, 2011

TO: Donna Griebel, M.D.
Director, Division of Gastroenterology Products
(HFD-180)

FROM: Gopa Biswas, Ph.D.
GLP and Bioequivalence Branch
Division of Scientific Investigations (DSI)

THROUGH: Martin K. Yau, Ph.D. *Martin K. Yau 2/24/11*
Acting Team Leader - Bioequivalence
GLP and Bioequivalence Branch
Division of Scientific Investigations

SUBJECT: Review of EIR Covering NDA 22-519 (b)(4) Tablets,
Ibuprofen 800 mg/Famotidine 26.6 mg sponsored by
Horizon Pharma, Inc.

At the request of the Division of Gastroenterology Products, the Division of Scientific Investigations (DSI) conducted inspections of the clinical and analytical portions of the following bioequivalence study:

Study Number: HZ-CA-0-15

Study Title: "A Randomized, Three-Period Crossover, Oral, Single-Dose, Open-Label Study to Determine the Bioequivalence of Famotidine and Ibuprofen in the Phase 3 and (b)(4) Formulations of HZT 501, and to Determine the Bioequivalence of Ibuprofen in the Phase 3 and (b)(4) Formulations of HZT-501 to an Equivalent Dose of Commercially Available Ibuprofen, in Fasted, Healthy, Adult Subjects"

The inspection of the clinical study was conducted at Cetero Research, St. Charles, MO (11/22-11/24/2010). Following the inspection, Form FDA-483 was issued (Attachment 1). The firm's written response was received by DSI on 1/25/2011 (Attachment 2). Our evaluation of the objectionable items and the firm's response follows:

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/s/

GOPA BISWAS
02/24/2011

MARTIN K YAU
02/25/2011



DEPARTMENT OF HEALTH & HUMAN SERVICES

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

M E M O R A N D U M

Date: November 24, 2010

From: Alyson Karesh, M.D., Medical Officer PMHS

Through: Hari Cheryl Sachs, M.D., Team Leader PMHS
Lisa Mathis, M.D., OND Associate Director

Drug: ibuprofen/famotidine (b) (4), HZT-501
Sponsor: Horizon Therapeutics, Inc.
NDA: 22-519

Dosage form: fixed dose, combination, immediate release, oral tablet containing 800 mg ibuprofen and 26.6 mg famotidine

Proposed dosage and administration: One (b) (4) (ibuprofen 800 mg and famotidine 26.6 mg) tablet administered orally three times per day

Proposed indication for adults (b) (4): Reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen.

(b) (4)

Consulted by: Division of Gastroenterology Products (DGP)
DGP Medical Officer: Ali Niak
DGP Team Lead: Lynne Yao
DGP RPM: Todd Phillips
PMHS PM: Matt Bacho

Consult Request

“The product (HZT-501) in this NDA is a fixed combination NSAID (ibuprofen, 800 mg)/H2RA (famotidine, 26.6 mg). The Sponsor’s proposed indication is the risk-reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen (b) (4) (b) (4)

On October 18, 2010, OSE completed a Pediatric Drug Use Review that revealed a large number of ibuprofen 800 mg prescriptions written for pediatric patients in the U.S. In pediatric patients aged 12-17 years, approximately (b) (4) prescriptions (3% of total prescriptions) were written in 2009... (b) (4)

. The Division requests PMHS evaluation and comment on the Division’s proposal. The Division is scheduled to attend the PeRC on December 8, 2010.”

Reviewer’s Comments: On verbal discussion with Lynne Yao (DGP, TL) Dr. Yao explained that DGP would like to know from PMHS whether, under PREA, DGP can require the Sponsor to make an age-appropriate formulation with respect to both the drug form (for example, a liquid for young children) and the drug strength (for example, a strength appropriate for young children). If, in fact, DGP can require the Sponsor to make an age-appropriate formulation with respect to both form and strength, then DGP would likely do so.

Background

The Division of Gastroenterology Products (DGP) is currently evaluating NDA 22-519, a 505(b)(2) application for HZT-501, a tablet containing ibuprofen and famotidine.

1. Ibuprofen

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) is the active ingredient in multiple prescription and OTC products. OSE evaluated the use of ibuprofen 800 mg in 12-17 year old patients in the outpatient retail setting,¹ and concluded that approximately (b) (4) prescriptions were filled by approximately (b) (4) patients in 2009.

(Brief background information about OTC and prescription ibuprofen is provided below². See Appendix IV for additional background information.)

OTC Ibuprofen²:

Ibuprofen is approved for OTC use in patients \geq 6 months for relief of minor aches and pains and temporary relief of fever. Approved OTC formulations in children $<$ 12 years include concentrated drops (e.g., NDAs 20-603 and 20812, 50 mg/1.25 ml) for patients 6- $<$ 24 months, oral suspension (e.g., NDAs 20-516 and 20-589, 100 mg/5 ml) and chewable tablets (e.g., NDAs 20-601, and 20-944, 100 mg) for patients 2-11 years and caplets (e.g., NDAs 20-267 and 20-602, 100 mg) for patients age 6-11 years. The 200 mg tablet (e.g. NDAs 18-989 and 19-012) is approved for these indications in patients

¹ NDA 22-519, OSE RCM# 2010-2148, Ibuprofen 800 mg Pediatric Drug Use Review, October 18, 2010.

² PMHS consult on ibuprofen by Elizabeth Durmowicz. February 17, 2010.

≥12 years. The recommended dosing regimens for OTC ibuprofen in patients 6 months-11 years are weight and/or age based, and dosing in patients ≥12 years is the same for adults and children, i.e. 200-400 mg every 4-6 hours as needed. The 200 mg tablet formulation is marketed by Wyeth as an “Adult Product”, whereas the other formulations are marketed as “Children’s Products”¹.

Advil[®] Migraine (NDA 20-402, Wyeth), Motrin[®] Migraine Pain (NDA 19-012, McNeil) and Migraine Relief (NDA 21-472, Banner) contain 200 mg ibuprofen as a single active ingredient and are approved for OTC use to treat migraine in adult patients. Labeling provides directions for use for adults, but for patients under 18 years, labeling states “ask a doctor”. The product manufactured by Banner has a PREA requirement to study migraine in patients 12-17 years.

Reviewer’s comments: There appears to be inconsistency in the duration of use for OTC ibuprofen products. Advil does not limit use³, but Motrin does with the statement, “Do not take longer than 10 days, unless directed by a doctor.”⁴

Prescription Ibuprofen²:

Ibuprofen in tablet and suspension formulations is approved for prescription use and carries a boxed warning for cardiovascular and gastrointestinal risk. The tablet formulations of ibuprofen (e.g. NDA 17-463 400 mg, 600 mg and 800 mg) are approved for prescription use in adult patients for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, mild to moderate pain and treatment of primary dysmenorrhea in dosages of 1200mg-3200 mg daily. Pediatric Use states: “Safety and effectiveness of [ibuprofen or brand name] tablets in pediatric patients have not been established”.

Ibuprofen suspension (100 mg/5 ml) is approved for prescription use in pediatric patients for relief of signs and symptoms of juvenile arthritis, and for relief of mild to moderate pain and reduction of fever in patients 6 months-2 years. Pediatric dosing is weight and indication based. The recommended treatment for juvenile arthritis is 30-40 mg/kg/day divided into three or four doses, for pain is 10 mg/kg/dose every 6-8 hours (maximum daily dose 40 mg/kg/day) and for fever is 5 or 10 mg/kg/dose depending on the temperature level (maximum daily dose 40 mg/kg). Prescription labeling for ibuprofen suspension includes PK and clinical trial data on studies in children 6 months- 12 years with fever primarily due to viral illness.

2. Famotidine

Famotidine, a histamine H₂-receptor antagonist, is the active ingredient in prescription and OTC products. There are no outstanding PREA requirements for famotidine.⁵

OTC Famotidine:

OTC Pepcid AC⁶ (NDA 20-325, NDA 20-801) is labeled to relieve heartburn associated with acid indigestion and sour stomach, and to prevent heartburn associated with acid

³ Advil.com. Accessed November 22, 2010.

⁴ Motrin.com. Accessed November 22, 2010.

⁵ FDA Postmarket Requirements and Commitments web site. Accessed November 19, 2010.

indigestion and sour stomach brought on by eating and drinking certain food and beverages. Dosing directions are provided for adults and children 12 years and older. OTC labeling states for children under 12 years of age, ask a doctor.

Prescription Famotidine:

Although prescription famotidine is approved for use in all ages, dosage information is not provided for all of the approved indications. For example, prescription Pepcid[®] tablets (NDA 19-462) and for oral suspension (NDA 19-527) is indicated in:

1. Short-term treatment of active duodenal ulcer.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.
3. Short-term treatment of active benign gastric ulcer.
4. Short-term treatment of gastroesophageal reflux disease (GERD) and the short-term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy.
5. Treatment of pathological hypersecretory conditions.

However, labeling provides pediatric dosing information (including for patients less than 3 months of age⁷) only for the GERD indication.

Reviewer's comment: Famotidine does not appear to be approved for chronic use in pediatric patients.

The Sponsor's Pediatric Drug Development Program

(b) (4)⁸ DGP recommended that the sponsor submit a deferral request with a pediatric plan, and a partial waiver request with justification.⁹ In addition, DGP explained to the sponsor that there was the "possibility that the efficacy of HZT-501 may be extrapolated from adults"⁹ and requested data to support that the disease course and treatment effect are reasonably similar in pediatric and adult patients (b) (4). Subsequently, Horizon Therapeutics, Inc. submitted (b) (4)

⁶ Pepcid AC (famotidine) tablet, film coated. DailyMed. Accessed November 22, 2010.

⁷ NDA 19-527. Pepcid, famotidine tablets and for oral suspension labeling approved November 5, 2007. Drugs@FDA, accessed November 17, 2010.

⁸ (b) (4)

NDA 22-519, Correspondence. Finalized October 22, 2010.

Request and Justification for a Partial Waiver^{10,11}

The sponsor is requesting a partial waiver of pediatric studies [REDACTED] (b) (4). Per the sponsor, the partial waiver is appropriate for each age cohort for the following reasons:

- Neonates: Studies are impossible or highly impractical because, per the sponsor, the number of pediatric patients is so small. Per the sponsor, Juvenile idiopathic arthritis (JIA) represents the largest pediatric population using ibuprofen chronically, and JIA does not usually present at birth.
- Infants up to 1 year, 11 months of age: Studies are impossible or highly impractical because the number of pediatric patients is so small. Per the sponsor, “Necessary studies for pediatric patients in this age range are impossible or highly impracticable because juvenile idiopathic arthritis does not usually present at birth and fewer than 2% of all pediatric visits to a physician for an NSAID prescription for arthritis and arthropathy occur in this age group.”¹⁰

- [REDACTED] (b) (4)

○

○



Reviewer comment: PMHS disagrees with the sponsor’s position that because HZT-501 [REDACTED] (b) (4)

Since HZT-501 will trigger PREA as a new active ingredient (a new combination of ibuprofen and famotidine), PREA requires the sponsor to submit an assessment of the product’s safety, effectiveness, dosing and administration for the claimed indication(s) in

¹⁰ NDA 22-519, Section 1.9.2, Request for Deferral of Pediatric Studies. November 10, 2010.

¹¹ NDA 22-519, Section 1.9.1, Request for Waiver of Pediatric Studies. November 10, 2010.

all relevant pediatric subpopulations [355c(a)(2)(A) Assessments/General]. Therefore, DGP may require the sponsor to evaluate age appropriate formulations, both with respect to drug strength and drug form (for example, a liquid), in pediatric patients.

The sponsor proposed language for labeling:

[REDACTED] (b) (4)

Reviewer comment:

[REDACTED] (b) (4)

PMHS Discussion of Proposed Waiver

[REDACTED] (b) (4)
[REDACTED]. PMHS recommends DGP consider requiring pediatric studies of patients as young 6 months of age depending on the indication (see below).

The decision to grant a waiver must be based upon one of the criteria outlined in the Pediatric Research Equity Act (PREA). Full or partial waivers must be granted if one of the three following criteria is met:

1. necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed),
2. there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups, OR
3. the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients, and is not likely to be used in a substantial number of pediatric patients

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

In the case of HZT-501, [REDACTED] (b) (4)

[REDACTED]

(b) (4)

Furthermore, per approved labeling, all patients taking NSAIDs are at risk for NSAID-associated gastric ulcers. Prescription ibuprofen labeling (400 mg, 600 mg, 800 mg tablets) boxed warning contains the following statement regarding the gastrointestinal risk associated with NSAID use: “NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms.”¹² (See Appendix I for full boxed warning.) Similarly, OTC labeling contains a “Stomach bleeding warning”. (See Appendix II for OTC ibuprofen warnings.) Therefore, if the indication is approved as proposed, then studies should not be limited to patients who use ibuprofen chronically or patients who already have NSAID-associated ulcers.

(b) (4), PMHS recommends DGP consider requiring studies down to age 6 months because famotidine is approved for use in all pediatric ages and ibuprofen is labeled for use in patients as young as 6 months of age.

For use in patients who require chronic therapy, PMHS recommends aligning the waiver and deferral request to match what is being required of JIA products, which is likely to be down to age 2 years.

PMHS defers to DGP whether extrapolation of efficacy from adults for ulcer prevention is acceptable. PMHS believes extrapolation of efficacy appears reasonable since although there are differences between pediatric and adult ibuprofen use, NSAID use puts both pediatric and adult patients at risk of developing upper gastrointestinal ulcers. Presuming extrapolation of efficacy is acceptable, the Sponsor’s plan will need to include data on long-term safety as well as the rationale for extrapolation. Input from clinical pharmacology is needed regarding the adequacy of existing pharmacokinetic data.

The Sponsor’s Deferral Request with Pediatric Plan Deferral Request¹⁰

The sponsor is requesting a deferral of pediatric studies (b) (4) because adult studies are completed and ready for approval for use in adults.

Reviewer’s comments: Although the reason for deferral appears reasonable to PMHS, PMHS recommends that younger patients be studied.

Pediatric Plan¹⁰

The sponsor is proposing a 6-month (24-week), multicenter, open-label safety study in patients (b) (4) of age who require treatment with NSAIDs. The sponsor is proposing to extrapolate efficacy from adults with the rationale

¹² Perrigo Ibuprofen (ibuprofen) tablet, Rx only, ANDA. Dailymed, accessed November 17, 2010.

that, the disease course and effect of treatment are “reasonably similar” in pediatric and adult patients. (See Appendix III for details of the sponsor’s proposed safety study.)

Reviewer’s comments:

- *The sponsor’s plan is incomplete since the required specific dates were not included. A pediatric plan is the applicant’s statement of intent describing the planned or ongoing pediatric studies, and must contain a timeline for the completion of studies. FDA recommends that the timeline include the dates the applicant will: (1) submit the protocol, (2) complete the studies, and (3) submit the study reports. The proposed plan is incomplete as the required timelines have not been provided.*
- *PMHS defers to DGP on whether the efficacy of HZT-501 for ulcer prevention in pediatric patients can be extrapolated from adults and the age cut for which extrapolation would be appropriate. PMHS believes extrapolation of efficacy appears reasonable since although there are differences between pediatric and adult ibuprofen use, NSAID use puts both pediatric and adult patients at risk of developing upper gastrointestinal ulcers. If efficacy can be extrapolated, the studies will need to include sufficient information regarding the safety of chronic use of this proposed combination.*
- *PMHS defers to DGP and the clinical pharmacology team in determining if PK studies are needed in pediatric patients.*

- [REDACTED] (b) (4)

PMHS Conclusions

PMHS agrees with DGP’s proposal [REDACTED] (b) (4)

[REDACTED] Furthermore, because DGP can require the sponsor to evaluate HZT-501 in patients of all ages, and because both famotidine and ibuprofen are approved for use in patients as young as 6 months of age, then based on the current proposed indication, PMHS recommends DGP defer pediatric studies for patients 6 months of age and older, and grant a partial waiver only for patients under 6 months of age. The sponsor would need to provide data on the use of ibuprofen in the younger age groups to support their waiver request. Should the indication be restricted to patients chronically using ibuprofen, PMHS recommends deferring pediatric studies down to age 2 years and granting a partial waiver from birth to 1 year, 11 months of age. The Sponsor would need to provide data on the use of ibuprofen and incidence of JIA to support their waiver request.

Although the pediatric plan the sponsor submitted only addresses patients [REDACTED] (b) (4) [REDACTED] if the sponsor submits the required dates (Protocol submission date, Study completion date, and Final report submission date), then their plan will be complete even if DGP wants younger patients studied. DGP can either ask the sponsor to submit a revised pediatric plan encompassing the younger aged patients, or due to time-constraints, DGP can opt to modify the plan themselves. Either way, when DGP

ultimately presents their proposal to the Pediatric Review Committee (PeRC) prior to NDA approval, DGP should present the pediatric study(ies) they want to require under PREA. PMHS is happy to assist with the PeRC paperwork if questions arise.

If the sponsor is not able to create an age appropriate formulation, then the sponsor must demonstrate that their reasonable attempts to produce an age appropriate formulation failed, and this data must be submitted to the Agency in a format for public posting.

APPENDIX I

Prescription Ibuprofen Boxed Warning^{12,13}

Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (see [WARNINGS](#) and **CLINICAL STUDIES**).
- Ibuprofen tablets are contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see [WARNINGS](#)).

Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (see [WARNINGS](#)).

¹³ NDA 17-463/s105, Motrin (ibuprofen) tablets. Labeling with effective date January 20, 2007.

APPENDIX II

OTC Ibuprofen Warnings¹⁴

Warnings

Allergy alert: Ibuprofen may cause a severe allergic reaction, especially in people allergic to aspirin. Symptoms may include:

- hives
- facial swelling
- asthma (wheezing)
- shock
- skin reddening
- rash
- blisters

If an allergic reaction occurs, stop use and seek medical help right away.

Stomach bleeding warning: This product contains an NSAID, which may cause severe stomach bleeding. The chance is higher if you

- are age 60 or older
- have had stomach ulcers or bleeding problems
- take a blood thinning (anticoagulant) or steroid drug
- take other drugs containing prescription or nonprescription NSAIDs [aspirin, ibuprofen, naproxen, or others]
- have 3 or more alcoholic drinks every day while using this product
- take more or for a longer time than directed

Do not use

- if you have ever had an allergic reaction to any other pain reliever/fever reducer
- right before or after heart surgery

Ask a doctor before use if

- stomach bleeding warning applies to you
- you have problems or serious side effects from taking pain relievers or fever reducers
- you have a history of stomach problems, such as heartburn
- you have high blood pressure, heart disease, liver cirrhosis, kidney disease, or asthma
- you are taking a diuretic

Ask a doctor or pharmacist before use if you are

- under a doctor's care for any serious condition
- taking aspirin for heart attack or stroke, because ibuprofen may decrease this benefit of aspirin
- taking any other drug

When using this product

- take with food or milk if stomach upset occurs
- the risk of heart attack or stroke may increase if you use more than directed or for longer than directed

¹⁴ Advil® Tablets, Drug Facts. Advil.com. Accessed November 22, 2010.

Stop use and ask a doctor if

- you experience any of the following signs of stomach bleeding:
 - feel faint
 - vomit blood
 - have bloody or black stools
 - have stomach pain that does not get better
- pain gets worse or lasts more than 10 days
- fever gets worse or lasts more than 3 days
- redness or swelling is present in the painful area
- any new symptoms appear

If pregnant or breast-feeding, ask a health professional before use. It is especially important not to use ibuprofen during the last 3 months of pregnancy unless definitely directed to do so by a doctor because it may cause problems in the unborn child or complications during delivery.

Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

APPENDIX III

Sponsor's Proposed Safety Study¹⁰

Study design:

Route of administration:

Dosage to be studied:

Pediatric patient population:

Number of patients:

Inclusion criteria:

Exclusion criteria:

Safety Variables:

Statistical Information:

(b) (4)

APPENDIX IV

Ibuprofen – Additional Background Information²

Regulatory Background:

Although initially approved in the US in 1974 as a prescription product for the treatment of symptoms associated with rheumatoid arthritis and osteoarthritis in adults, ibuprofen, a non-steroidal anti-inflammatory drug with analgesic and antipyretic activities, has been available OTC for the relief of minor aches and pains and for fever reduction in patients 12 years and older (200-400 mg/dose, maximum daily dose of 1,200 mg) since 1984. Pediatric formulations have been available by prescription since 1989 and available for OTC use with dosing for children 2 years to less than 12 years since 1995. Safety studies completed in response to a Written Request (WR) resulted in OTC product labeling for ibuprofen infant drops and prescription labeling for ibuprofen oral suspension in patients 6 months to <2 years for temporary reduction of fever and relief of minor aches and pains. Exclusivity was granted to McNeil (Motrin oral suspension (NDA 20-516) and drops (NDA 20-603) in July 1998 (exclusivity expires June 20, 2012) and to Whitehall-Robbins (Advil oral suspension (NDA 20-589) and drops (NDA 20-812) in September 2001 (exclusivity expired).

Ibuprofen is currently available both by prescription and OTC (see below), and is regulated as a new drug. More than 30 NDAs/ANDAs for OTC marketing of ibuprofen 200 mg tablets are listed on the Drugs@FDA website.

On August 21, 2002, in response to a citizen's petition filed in 1997, FDA published a proposed rulemaking (67 FR 54139) to amend the IAAD tentative final monograph (TFM) issued in November 1988 to include ibuprofen as a GRASE (generally recognized as safe and effective) analgesic/antipyretic active ingredient for OTC adult use as a single ingredient only. However, interim marketing while the rule is being finalized was not provided. As a result, OTC ibuprofen continues to be marketed only under approved NDAs and ANDAs.

Banner Pharmacaps has a PREA PMR to study ibuprofen 200 mg liquid gel in the treatment of migraine in patients 12-16 years and the sponsor of Caldolor, an intravenous (IV) ibuprofen product approved in June 2009 for the management of pain and reduction of fever in adults, has a PREA PMR for patients 0-16 years for these indications. In addition, in March 2009, a WR was issued for studies of the IV product in pediatric patients with fever to determine the pharmacokinetic (PK) and safety of IV ibuprofen in patients 0-16 years and the efficacy of IV ibuprofen in patients <6 months.

Background Drug Information:

OTC Ibuprofen:

Ibuprofen is approved for OTC use in patients \geq 6 months for relief of minor aches and pains and temporary relief of fever. Approved OTC formulations in children < 12 years include concentrated drops (e.g., NDAs 20-603 and 20812, 50 mg/1.25 ml) for patients 6-

<24 months, oral suspension (e.g., NDAs 20-516 and 20-589, 100 mg/5 ml) and chewable tablets (e.g., NDAs 20-601, and 20-944, 100 mg) for patients 2-11 years and caplets (e.g., NDAs 20-267 and 20-602, 100 mg) for patients age 6-11 years. The 200 mg tablet (e.g. NDAs 18-989 and 19-012) is approved for these indications in patients ≥ 12 years. The recommended dosing regimens for OTC ibuprofen in patients 6 months-11 years are weight and/or age based, and dosing in patients ≥ 12 years is the same for adults and children, i.e. 200-400 mg every 4-6 hours as needed. The 200 mg tablet formulation is marketed by Wyeth as an “Adult Product”, whereas the other formulations are marketed as “Children’s Products”¹.

Advil[®] Migraine (NDA 20-402, Wyeth), Motrin[®] Migraine Pain (NDA 19-012, McNeil) and Migraine Relief (NDA 21-472, Banner) contain 200 mg ibuprofen as a single active ingredient and are approved for OTC use to treat migraine in adult patients. Labeling provides directions for use for adults, but for patients under 18 years, labeling states “ask a doctor”. The product manufactured by Banner has a PREA requirement to study migraine in patients 12-17 years.

The original OTC approval for ibuprofen 200 mg (NDA 19-012) in patients ≥ 12 years occurred in 1984 and was based on pivotal studies of minor aches and pains secondary to four conditions, i.e. dysmenorrhea, post-partum pain, dental pain and headache, and supportive data on use in osteoarthritis and rheumatoid arthritis (summarized from data on the prescription strength ibuprofen product approved in adult patients, NDA 17-463, and literature review), data from a trial for use in general musculoskeletal injuries (subjects were students from a “major university” with a variety of minor conditions), clinical trial data and literature summary on antipyretic use, and a “literature review concerning use in children”. In the original application, the Sponsor noted that “the world literature gives a number of reports on ibuprofen” and “these authors report positive pediatric experience with ibuprofen”. The Sponsor also stated that pediatric dosages have not been clearly established.

The data to support dosing, safety and efficacy for the OTC indications in pediatric patients <12 years have been obtained more recently. The analgesic indication for patients 2-<12 years was granted in 1995 based on data from 4 adequate and well-controlled trials in children 5-12 years with otitis media and sore throat. Approval for the use of ibuprofen for pain and fever in patients >6 months-2 years was granted based on bioequivalence of the infant drop formulation and safety and efficacy supported by the literature, especially data from the Boston Fever Study⁹ and the Children’s Analgesic Medicine Project (CAMP)². The safety database in the literature for children less than 12 years includes >100,000 patients. Of note, cited by experts and used for approval in support of the safe use of ibuprofen in pediatric patients, the Boston Fever Study (n >84,000 patients < 12 years with fever)⁹ and the Children’s Analgesic Medicine Project (CAMP, n >30,000 patients < 12 years with fever or pain)² evaluated patients treated with ibuprofen compared to acetaminophen.

Prescription Ibuprofen:

Ibuprofen in tablet and suspension formulations is approved for prescription use and carries a boxed warning for cardiovascular and gastrointestinal risk. The tablet formulations of ibuprofen (e.g. NDA 17-463 400 mg, 600 mg and 800 mg) are approved for prescription use in adult patients for relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis, mild to moderate pain and treatment of primary dysmenorrhea in dosages of 1200mg-3200 mg daily. Minimal data about PK and clinical studies are provided in labeling. Pediatric Use states: "Safety and effectiveness of [ibuprofen or brand name] tablets in pediatric patients have not been established".

Ibuprofen suspension (100 mg/5 ml) is approved for prescription use in pediatric patients for relief of signs and symptoms of juvenile arthritis, and for relief of mild to moderate pain and reduction of fever in patients 6 months-2 years. Pediatric dosing is weight and indication based. The recommended treatment for juvenile arthritis is 30-40 mg/kg/day divided into three or four doses, for pain is 10 mg/kg/dose every 6-8 hours (maximum daily dose 40 mg/kg/day) and for fever is 5 or 10 mg/kg/dose depending on the temperature level (maximum daily dose 40 mg/kg). Prescription labeling for ibuprofen suspension includes PK and clinical trial data on studies in children 6 months- 12 years with fever primarily due to viral illness.

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/s/

ALYSON R KARESH
12/02/2010

HARI C SACHS
12/03/2010
I agree with the recommendations

LISA L MATHIS
12/14/2010

DSI CONSULT: Request for Clinical Inspections

Date: December 10, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ali Niak, MD, Medical Officer, Division of Gastroenterology
Lynne Yao, MD, Medical Officer, Acting Team Leader, Division of
Gastroenterology

From: Todd Phillips, PharmD, Regulatory Project Manager, Division of
Gastroenterology

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022519
Applicant: Horizon Pharma, Inc.
Applicant contact information (to include phone/email):
Timothy P. Walbert
President and CEO
T: 224-383-3009
1033 Skokie Boulevard, Suite 355
Northbrook, IL 60062
twalbert@horizonpharma.com

Drug Proprietary Name: Duexis (ibuprofen/famotidine) Tablets

NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication:
DSI Consult

Reference ID: A62008
2876100

Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen

PDUFA: January 21, 2011

Action Goal Date: Anticipate taking a Major Amendment in December 2010, resulting in a new PDUFA of April 22, 2011

Inspection Summary Goal Date: February 18, 2011

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 340 Vrijendra Kumar, M.D. Advanced Biomedical Research of America 8420 South Eastern Avenue Suite 102 Las Vegas, NV 89123	HZ-CA-303	35	Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen
Site 363 Dennis Riff, M.D. Advanced Clinical Research Institute 1211 W. La Palma Ave. Suite 602, 306, 303 Anaheim, CA 92801	HZ-CA-303	76	Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other: For sites 340 and 363, there were a large number of patients who early terminated or had early terminations without ulcer.

International Inspections:

Reasons for inspections (please check all that apply): **NA**

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact *Todd Phillips* at 301-796-4857 or *Ali Niak* at 301-796-2156.

Concurrence: (as needed)

<u>Lynne Yao</u>	Medical Team Leader
<u>Ali Niak</u>	Medical Reviewer
_____	Division Director (for foreign inspection requests or requests for 5 or more sites only)

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

/s/

TODD D PHILLIPS
12/10/2010

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

Date: November 22, 2010
Application Type/Number: NDA 022519
To: Donna Griebel, MD, Director
Division of Gastroenterology Products
Through: Zachary Oleszczuk, Pharm.D., Team Leader
Denise Toyer, Pharm.D., Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Error Prevention and Analysis
From: Yelena Maslov, Pharm.D., Safety Evaluator
Division of Medication Error Prevention and Analysis
Subject: Label and Labeling Review
Drug Name(s): Duexis (Ibuprofen and Famotidine) Tablets, 800 mg/26.6 mg
Applicant/sponsor: Horizon Therapeutics
OSE RCM #: 2010-1390

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1 INTRODUCTION

This review responds to a request from the Division of Gastroenterology Products, dated May 10, 2010 for DMEPA evaluation of the container label and package insert labeling for Horizon's Duexis Tablets for their potential to contribute to medication errors.

1.1 REGULATORY HISTORY

Duexis (Ibuprofen and Famotidine) Tablets 800 mg/26.6 mg is a 505 (b)(2) application, NDA 022519, submitted to the FDA on March 23, 2010. The application references Motrin Tablets (NDA 017463) and Pepcid Tablets (NDA 019462).

DMEPA found the proprietary name (b) (4) unacceptable in RCM OSE review #2009-2447, dated May 24, 2009, for this product. The Applicant then submitted the name 'Duexis' July 9, 2010. The new name, Duexis, was found to be vulnerable to name confusion that could lead to medication errors with (b) (4)*** a proposed proprietary name of a pending NDA (022522) under review with the Agency. Therefore, at this time, the acceptability of the proposed proprietary name, Duexis, is dependent upon which application is approved first.

2 METHODS AND MATERIALS

We use Failure Mode and Effects Analysis¹ (FMEA) and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling. We provide recommendations that aim at reducing the risk of medication errors.

This review focused on the Duexis Tablets container label, package insert, and medication guide labeling submitted by the Applicant on July 9, 2010 (See Appendix A for the container label image):

- Container Label: 90 Tablets

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the proposed container label and package insert labeling noted areas where information can be clarified and improved to minimize the potential of medication errors. Section 3.1 *Comments to the Division* contains our recommendations regarding package insert labeling. Section 3.2 *Comments to the Applicant* contains our recommendations for the container labels and the carton labeling. We request the recommendations in Section 3.2 be communicated to the Applicant prior to approval.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact OSE Regulatory Project Manager Nitin Patel at 301-796-5412.

3.1 COMMENTS TO THE DIVISION

1. Throughout the package insert labeling, the strength is embedded in the established name (b) (4). Typically, the strength appears outside of

¹ Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

*** This document contains proprietary and confidential information that should not be released to public

the parentheses with the established name. Revise the presentation of the strength, so that it is not embedded in the established name. See example below:

Duexis (Ibuprofen and Famotidine) Tablets 800 mg/26.6 mg

2. Highlights of Prescribing Information and Full Prescribing Information, *Dosage and Administration Section*

Relocate Section 5.15 *Information for Patients*, which contains the following statements: “Tablets should be swallowed whole. Do not chew, divide, or crush tablets” to the *Dosage and Administration Section* in Highlights of Prescribing Information and Full Prescribing Information immediately after the recommended daily dose statement.

3.2 COMMENTS TO THE APPLICANT

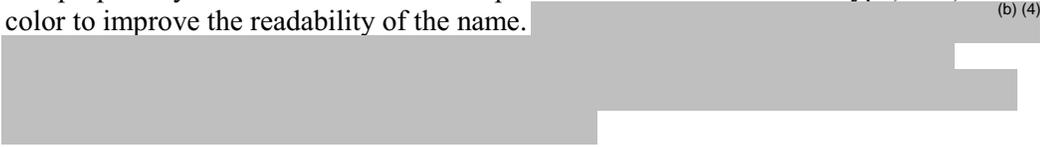
A. Container Label

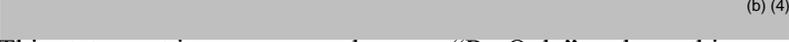
1. Ensure the size of the established name is at least ½ the size of the letters comprising the proprietary name and has prominence consistent with the proprietary name (type, size, color, font) in accordance with 21 CFR 201.10 (g)(2)
2. Revise the presentation of the established name and strength on the principle display panel so that the dosage form is present in accordance with USP recommendations and the product strength follows the dosage form.

The United States Pharmacopeia General Chapter <1121> requirements that states: *For a variety of dosage forms, titles are in the following general form: [DRUG] [ROUTE OF ADMINISTRATION] [DOSAGE FORM]. The term for route of administration is omitted for those dosage forms for which the route of administration is understood. The general form then becomes simply [DRUG] [DOSAGE FORM].*

Thus, the proprietary name, established name, dosage form, and strength should be presented as follows:

Duexis
(Ibuprofen and Famotidine) Tablets
800 mg/26.6 mg

3. The proprietary name ‘Duexis’ should be presented in a consistent font type, size, and color to improve the readability of the name. (b) (4)

4. Add a prominently displayed, bolded Medication Guide statement to the principle display panel in accordance with 21 CFR 208.24. You can include the following statement or similar: “ATTENTION PHARMACIST: Dispense attached Medication Guide to each patient”.
5. Delete or relocate and decrease font size of the graphic featuring the Applicant’s name from the principle display panel to the side panel. As currently presented, this graphic competes for prominence with proprietary and established names of the product, does not convey any important information, and occupies space.
6. Add the statements (b) (4) to the principle display panel in place of the graphic featuring the Applicant’s name to emphasize the correct administration of the product

7. Delete the statement  (b) (4) from the side panel. This statement is unnecessary because “Rx Only” replaces this cautionary statement and appears on the principle display panel.

Appendix A: Duexis Container Label



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

/s/

YELENA L MASLOV
11/22/2010

ZACHARY A OLESZCZUK
11/22/2010

CAROL A HOLQUIST on behalf of DENISE P TOYER
11/22/2010
For Denise Toyer

CAROL A HOLQUIST
11/22/2010



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

Date: October 18, 2010

To: Lynne Yao, MD
Medical Officer
Division of Gastroenterology Products, OND
Office of Drug Evaluation III

Through: Grace Chai, PharmD
Acting Drug Use Data Analyst Team Leader

Laura Governale, Pharm.D
Drug Use Data Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology

From: Patty Greene, Pharm.D
Drug Use Data Analyst
Division of Epidemiology
Office of Surveillance and Epidemiology

Subject: Ibuprofen 800 mg Pediatric Drug Use Review

Drug Name(s): (b) (4) tablets (ibuprofen 800 mg/famotidine 26.6 mg)

Application Type/Number: NDA 22-519

Applicant/sponsor: Horizon Pharma

OSE RCM #: 2010-2148

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

INTRODUCTION

The Division of Gastroenterology Products (DGP) is evaluating a (b) (4) submitted by the sponsor of (b) (4) tablets (ibuprofen 800 mg/famotidine 26.6 mg) (b) (4)

In response to safety concerns regarding off-labeled use of ibuprofen 800 mg tablets in pediatric patients, DGP requests drug use data to provide an estimate of pediatric use in the outpatient setting. In support of that assessment, this review describes drug utilization patterns among pediatric patients aged 0-11, 12-17 years and adults 18 years or older during from January 1, 2007 through August 31, 2010.

1 METHODS AND MATERIALS

1.1 DETERMINING SETTINGS OF CARE

IMS Health, IMS National Sales Perspectives™ was used to determine the various retail and non-retail channels of distribution for ibuprofen. Sales data for the 12-month period ending August 2010 indicated that approximately (b) (4) of ibuprofen packages (Eaches) were distributed to outpatient retail pharmacies; (b) (4) were to non-retail settings; and less than (b) (4) were to mail order pharmacies.¹ As a result, outpatient retail utilization patterns were examined. Neither mail order nor non-retail settings data were included in this analysis.

1.2 DATA SOURCES USED

Proprietary drug use databases licensed by the Agency were used to conduct this analysis (see Appendix 1 for full data description).

SDI, Vector One®: National (VONA) was used to obtain estimates of the number of outpatient dispensed prescriptions for ibuprofen 800 mg tablets, stratified by age (0-11, 12-17, 18+ years), from January 2007 to August 2010. SDI, Vector One®: Total Patient Tracker (TPT) was used to obtain estimates of the number of patients receiving a dispensed prescription for ibuprofen 800 mg tablets, stratified by age (0-11, 12-17, 18+ years), in the outpatient settings from January 2007 to August 2010.

2 RESULTS

2.1 OUTPATIENT DISPENSED PRESCRIPTIONS

Table 1 provides the total number of dispensed prescription for ibuprofen 800 mg tablets by patient age (0-11, 12-17 and 18+ years) in outpatient retail pharmacies from January 2007 to August 2010. Overall, prescription utilization increased by approximately (b) (4) from (b) (4) prescriptions in year 2007 to (b) (4) prescriptions in year 2009. Adult patients aged 18 years and older accounted for the majority of the prescription share with approximately (b) (4) prescriptions (b) (4) of total share) in year 2009. Prescription utilization in pediatric patients aged 12-17 years decreased by approximately (b) (4) for the review period from approximately (b) (4) prescriptions (b) (4) of total share) to approximately (b) (4)

¹ IMS Health, IMS National Sales Perspectives™. Extracted October 2010. File: 1010ibup.xls

dispensed prescriptions (b) (4) of total share) in year 2009. Approximately (b) (4) prescriptions (b) (4) of total share) were dispensed to pediatric patients in the 0-11 year age group in year 2009.

Table 1. Total dispensed prescriptions for Ibuprofen 800mg by patient age (0-11, 12-17, 18+) in U.S. outpatient retail pharmacies, January 1, 2007 - August 31, 2010

(b) (4)

2.2 PROJECTED PATIENTS

Table 2 provides the total number of projected patients for ibuprofen 800 mg tablets by patient age in outpatient retail pharmacies from January 2007 to August 2010. Trends for patient data were similar to prescription data. Adult patients aged 18 years and older accounted for the majority of the patient share with (b) (4) patients (b) (4) of total patients) in year 2009. Pediatric patients aged 12-17 years remained relatively fixed from (b) (4) patients in year 2007 to approximately (b) (4) patients in year 2009. Nearly (b) (4) patients (b) (4) of total patients) received a dispensed prescription for ibuprofen among pediatric patients in the 0-11 year age group in year 2009.

Table 2. Total projected patients age (0-11, 12-17, 18+) who filled a prescription for Ibuprofen 800mg in U.S. outpatient retail pharmacies, January 1, 2007 - August 31, 2010

(b) (4)

3 LIMITATIONS

Findings from this review should be interpreted in the context of the known limitations of the databases used. We estimated that ibuprofen was distributed primarily to the outpatient setting based on the IMS Health, IMS National Sales Perspectives™. These data do not provide a direct estimate of use but do provide a national estimate of units sold from the manufacturer into the various channels of distribution. The amount of product purchased by these non-federal hospital channels of distribution may be a possible surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use.

4 CONCLUSIONS

In the outpatient retail pharmacy setting, ibuprofen 800mg prescriptions dispensed to pediatric patients in the 12-17 year age group accounted for approximately (b) (4) prescriptions (b) (4) of total prescriptions) and approximately (b) (4) patients (b) (4) of total patients) in year 2009.

APPENDIX 1: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

SDI Vector One®: National (VONA)

SDI's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims per year, representing over 160 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. SDI receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

SDI Vector One®: Total Patient Tracker (TPT)

SDI's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

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/s/

TODD D PHILLIPS
10/22/2010

DSI CONSULT

Request for Biopharmaceutical Inspections

DATE: August 30, 2010

TO: Associate Director for Bioequivalence
Division of Scientific Investigations, HFD-48

THROUGH: Dennis Bashaw, Pharm.D.
Director, Division of Clinical Pharmacology 3, OCP/OTS

FROM: Todd Phillips
Regulatory Project Manager, Division of Gastroenterology Products,
HFD-180

SUBJECT: Request for Biopharmaceutical Inspections
NDA 22-519
(b) (4) Tablet Ibuprofen 800 mg/famotidine 26.6 mg
Horizon Pharma, Inc.

The following studies/sites pivotal to approval have been identified for inspection:

Study Title: A Randomized, Three-Period Crossover, Oral, Single- Dose, Open-Label Study to Determine the Bioequivalence of Famotidine and Ibuprofen in the Phase 3 and (b) (4) Formulations of HZT-501, and to Determine the Bioequivalence of Ibuprofen in the Phase 3 and (b) (4) Formulations of HZT-501 to an Equivalent Dose of Commercially Available Ibuprofen, in Fasted, Healthy, Adult Subjects

Study #	Clinical Site (name, address, phone, fax, contact person, if available)	Analytical Site (name, address, phone, fax, contact person, if available)
HZ-CA-0-15	Cetero Research-St Louis 400 Fountain Lakes Blvd. St. Charles, MO 63301 Principal investigator Ramon Vargus, MD, MPH Telephone: 636-757-7074	(b) (4)

GOAL DATE FOR COMPLETION:

We request that the inspections be conducted and the Inspection Summary Results be provided by November 21, 2010.

Should you require any additional information, please contact Todd Phillips at 301-796-4857.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

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/s/

TODD D PHILLIPS
08/30/2010

EDWARD D BASHAW
08/30/2010

DSI CONSULT: Request for Clinical Inspections

Date: June 09, 2010

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Ali Niak, MD, Medical Officer, Division of Gastroenterology
Lynne Yao, MD, Medical Officer, Acting Team Leader, Division of Gastroenterology

From: Todd Phillips, PharmD, Regulatory Project Manager, Division of Gastroenterology

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA-022519
Applicant: Horizon Pharma, Inc.
Applicant contact information (to include phone/email):
Timothy P. Walbert
President and CEO
T: 224-383-3009
1033 Skokie Boulevard, Suite 355
Northbrook, IL 60062
twalbert@horizonpharma.com

Drug Proprietary Name: (b) (4) (ibuprofen/famotidine) Tablets (PN denial letter issued: 24MAY2010)

NME or Original BLA (Yes/No): No
Review Priority (Standard or Priority): Standard

Study Population includes < 17 years of age (Yes/No): No
Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s):

Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen

PDUFA: January 21, 2011

Action Goal Date: January 21, 2011

Inspection Summary Goal Date: November 21, 2010

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 144 Leann Serbousek, MD Sooner Clinical Research 5929 North May Avenue Suite 401 Oklahoma City, OK 73112	HZ-CA-301	38	Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen
Site 180 William Abraham, MD Radiant Research, Inc. 7042 East Broadway Boulevard Tucson, AZ 85710	HZ-CA-301	22	Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen
Site 389 Vaughn Mancha, Jr., MD Montgomery Surgical Center 855 East South Blvd. Montgomery, AL 36116	HZ-CA-303	167	Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen

III. Site Selection/Rationale

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects (*SITES 389 and 144*)
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (*SITE 180*):
This site appears to have a higher rate of ulcers in the placebo group compared to other sites. Therefore, the results from this site may have influenced the overall results of the study.

International Inspections:

Reasons for inspections (please check all that apply): **NA**

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

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

IV. Tables of Specific Data to be Verified (if applicable)

NA

Should you require any additional information, please contact *Todd Phillips* at 301-796-4857 or *Ali Niak* at 301-796-2156.

Concurrence: (as needed)

<u>Lynne Yao</u>	Medical Team Leader
<u>Ali Niak</u>	Medical Reviewer
_____	Division Director (for foreign inspection requests or requests for 5 or more sites only)

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22519

ORIG-1

HORIZON PHARMA HZT-501
INC

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/s/

TODD D PHILLIPS
06/09/2010

RPM FILING REVIEW
(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements (except SE8 and SE9)

Application Information		
NDA # 022519 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (pending) Established/Proper Name: Ibuprofen/famotidine Dosage Form: Fixed-dose Combination Tablet Strengths: 800 mg ibuprofen / 26.6 mg famotidine		
Applicant: Horizon Pharma, Inc. Agent for Applicant (if applicable):		
Date of Application: March 23, 2010 Date of Receipt: March 23, 2010 Date clock started after UN:		
PDUFA Goal Date: January 21, 2011	Action Goal Date (if different):	
Filing Date: May 22, 2010	Date of Filing Meeting: May 7, 2010	
Chemical Classification: (1,2,3 etc.) (original NDAs only) 4		
Proposed indication(s)/Proposed change(s): Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen		
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" form found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027499.html and refer to Appendix A for further information.</i>		
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted	
<i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher was submitted, review classification is Priority.</i>		
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Drug/Device <input type="checkbox"/> Biologic/Device	
<input type="checkbox"/> Fast Track <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	<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)	

Other:	<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): 072116				
Goal Dates/Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If not, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	X			
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If not, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	X			
Are all classification properties [e.g., orphan drug, 505(b)(2)] entered into tracking system? <i>If not, ask the document room staff to make the appropriate entries.</i>	X			
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>		X		
If yes, explain in comment column.				
If affected by AIP, has OC/DMPQ been notified of the submission? If yes, date notified:				
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	X			
<u>User Fee Status</u> <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 UN letter and contact user fee staff.</i>	Payment for this application: <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			
<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>	Payment of other user fees: <input type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
Note: 505(b)(2) applications are no longer exempt from user fees pursuant to the passage of FDAAA. All 505(b) applications, whether 505(b)(1) or 505(b)(2), require user fees unless otherwise waived or exempted (e.g., small business waiver, orphan exemption).				

505(b)(2) (NDAs/NDA Efficacy Supplements only)		YES	NO	NA	Comment
Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?			X		
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 less than that of the reference listed drug (RLD)? (see 21 CFR 314.54(b)(1)).			X		
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))? <i>Note: If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9).</i>			X		
Is there unexpired exclusivity on the active moiety (e.g., 5-year, 3-year, orphan or pediatric exclusivity)? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm		X			
If yes, please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
N022348	Ibuprofen (solution; intravenous)	NP (new product)	June 11, 2012 (3-year exclusivity)		
N021903	Ibuprofen lysine (injectable; intravenous)	ODE (orphan)	April 13, 2013 (7-year exclusivity)		
<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 108(b)(2). Unexpired, 3 year exclusivity will only block the approval, not the submission of a 505(b)(2) application.</i>					
Exclusivity		YES	NO	NA	Comment
Does another product have orphan exclusivity for the same indication? Check the Electronic Orange Book at: http://www.fda.gov/cder/ob/default.htm			X		
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007)</i>				X	
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (NDAs/NDA efficacy supplements only) If yes, # years requested: 3-year WH exclusivity <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>		X			

Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?		X		
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact Mary Ann Holovac, Director of Drug Information, OGD/DLPS/LRB.</i>				

Format and Content				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance ¹ ? If not , explain (e.g., waiver granted).	X			
Index: Does the submission contain an accurate comprehensive index?	X			
Is the submission complete as required under 21 CFR 314.50 (<i>NDAs/NDA efficacy supplements</i>) or under 21 CFR 601.2 (<i>BLAs/BLA efficacy supplements</i>) including: <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.	X			
Controlled substance/Product with abuse potential: Is an Abuse Liability Assessment, including a proposal for scheduling, submitted? <i>If yes, date consult sent to the Controlled Substance Staff:</i>		X		
BLAs only: Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #				

Forms and Certifications				
<p><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></p>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature?	X			
<i>If foreign applicant, both the applicant and the U.S. agent must sign the form.</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	X			
Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a?	X			
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature?	X			
<i>Forms must be signed by the APPLICANT, not an Agent.</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	X			
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? (<i>Certification is not required for supplements if submitted in the original application</i>)	X			
<i>If foreign applicant, both the applicant and the U.S. Agent must sign the certification.</i>				
<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>				

Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
<p>For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?</p> <p><i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i></p> <p><i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i></p>	X			

Pediatrics	YES	NO	NA	Comment
<p><u>PREA</u></p> <p>Does the application trigger PREA?</p> <p><i>If yes, notify PeRC RPM (PeRC meeting is required)</i></p> <p><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></p>	X			Per Pediatric Page, a new combination is considered to be a new active ingredient
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>		X		
<p>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?</p> <p><i>If no, request in 74-day letter</i></p>	X			(b) (4)
<p>If a request for full waiver/partial waiver/deferral is included, does the application contain the certification(s) required under 21 CFR 314.55(b)(1), (c)(2), (c)(3)/21 CFR 601.27(b)(1), (c)(2), (c)(3)</p> <p><i>If no, request in 74-day letter</i></p>	X			
<p><u>BPCA</u> (NDAs/NDA efficacy supplements only):</p> <p>Is this submission a complete response to a pediatric Written Request?</p> <p><i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)</i></p>		X		

Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that it is submitted as a separate document and routed directly to OSE/DMEPA for review.</i>	X			PN review request submitted to IND 72116
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) <input 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 in 74-day letter.</i>	X			
Is the PI submitted in PLR format?	X			
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request PLR format in 74-day letter.</i>				
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to DDMAC?	X			
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? <i>(send WORD version if available)</i>	X			
REMS consulted to OSE/DRISK?			X	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA?	X			
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>				

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?				
Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) <i>If yes, specify consult(s) and date(s) sent:</i>		X		

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s) Date(s): May 18, 2006; March 18, 2008 <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s) Date(s): December 17, 2009 <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): No-agreement letter (August 25, 2006); Agreement letter (December 14, 2006) <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	X			

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

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 7, 2010

NDA#: 022519

PROPRIETARY NAME: (b) (4) (pending)

ESTABLISHED/PROPER NAME: Ibuprofen/famotidine

DOSAGE FORM/STRENGTH: Fixed-dose combination tablet, 800 mg ibuprofen / 26.6 mg famotidine

APPLICANT: Horizon Pharma, Inc.

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): Risk reduction of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen

BACKGROUND:

A Pre-IND meeting was held on 13JUN2005. At this meeting, the Agency informed the sponsor that, based upon their proposed indication, adequate and well-controlled efficacy trials would be required (as opposed to a bioequivalence trial). The sponsor submitted IND 72116 on 25JAN2006. An End-of-Phase 2 meeting was held on 18MAY2006. At this meeting, the Phase 3 clinical development plan was discussed (primary endpoint, inclusion/exclusion criteria, long-term safety exposure requirements, appropriate regulatory pathway, and nonclinical data requirements). On 25AUG2006, the Division issued a SPA no-agreement letter (primary efficacy endpoint). On 14DEC2006, the Division issued a SPA agreement letter. A Type B meeting to discuss the clinical pharmacology and CMC development programs occurred on 18MAR2008; topics of discussion included the clinical pharmacology study requirements (BE/BA, food-effect, and renal impairment studies) and CMC requirements. A Pre-NDA meeting was held on 17DEC2009; topics of discussion included the Phase 3 clinical trials results, BE study results, CMC data (drug substance/drug product), and submission format. The sponsor has utilized an alternative eCTD arrangement in which the clinical safety and efficacy summaries in Module 2 serve as the narratives for the ISS and ISE in Module 5. The sponsor submitted a request for Proprietary Name (b) (4) review to the IND on 23NOV2009 (OSE PDUFA Date: 5/23/2010).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Todd Phillips	Y
	CPMS/TL:	Wes Ishihara	N
Cross-Discipline Team Leader (CDTL)	Lynne Yao		Y

Clinical	Reviewer:	Ali Niak	Y
	TL:	Lynne Yao	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		
	TL:		

Clinical Pharmacology	Reviewer:	Jane Bai	Y
	TL:	Sue Chih Lee	Y
Biostatistics	Reviewer:	Wen-Jen Chen	Y
	TL:	Mike Welch	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Dinesh Gautam	Y
	TL:	Sushanta Chakder	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Gene Holbert	Y
	TL:	Marie Kowblansky	Y
Quality Microbiology (<i>for sterile products</i>)	Reviewer:		
	TL:		
CMC Labeling Review (<i>for BLAs/BLA supplements</i>)	Reviewer:		
	TL:		
Facility Review/Inspection	Reviewer:	Tara Goen	Y
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Shirley Zeigler	N
	TL:	Laura Pincock	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
Bioresearch Monitoring (DSI)	Reviewer:		
	TL:		

Other reviewers		
Other attendees		

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues? <p>If yes, list issues:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> • Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an original NME or BLA application, include the reason. For example:</i></p> <ul style="list-style-type: none"> ○ <i>this drug/biologic is not the first in its class</i> ○ <i>the clinical study design was acceptable</i> ○ <i>the application did not raise significant safety or efficacy issues</i> ○ <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p>BIOSTATISTICS</p> <p>Comments:</p>	<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
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p>IMMUNOGENICITY (BLAs/BLA efficacy supplements only)</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>PRODUCT QUALITY (CMC)</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

Comments:	
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<p><u>Environmental Assessment</u></p> <ul style="list-style-type: none"> • Categorical exclusion for environmental assessment (EA) requested? <p>If no, was a complete EA submitted?</p> <p>If EA submitted, consulted to EA officer (OPS)?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Quality Microbiology (for sterile products)</u></p> <ul style="list-style-type: none"> • Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> • Establishment(s) ready for inspection? ▪ Establishment Evaluation Request (EER/TBP-EER) submitted to DMPQ? <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<p><input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p><u>CMC Labeling Review (BLAs/BLA supplements only)</u></p> <p>Comments:</p>	<p><input type="checkbox"/> Review issues for 74-day letter</p>

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Division Director	
21st Century Review Milestones (see attached) (optional): Submission receipt: 23MAR2010 Submission Filing (Day 60): 22MAY2010 Communicate Filing Issues (Day 74): 04JUN2010 Mid-Cycle Meeting: 31AUG2010 Primary reviews complete: 10DEC2010 Secondary reviews complete: 15DEC2010 Communicate PMR/Labeling to Sponsor: 17DEC2010 CDTL review complete: 22DEC2010 Action Package to Division Director: 05JAN2011 Action Date: 21JAN2011	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that the review and chemical classification properties, as well as any other pertinent properties (e.g., orphan, OTC) are correctly entered into tracking system.
<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"/>	
<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 DMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Other

Appendix A (NDA and NDA Supplements only)

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely

for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),
- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your OND ADRA or OND IO.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22519

ORIG-1

HORIZON PHARMA HZT-501
INC

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

/s/

TODD D PHILLIPS
05/20/2010

RICHARD W ISHIHARA
05/20/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Gastroenterology Products

Application Number: NDA 022519

Name of Drug: HZT-501 (ibuprofen/famotidine) Tablets, 800 mg/26.6 mg

Applicant: Horizon Therapeutics, Inc.

Material Reviewed:

Submission Date: March 23, 2010

Receipt Date(s): March 23, 2010

Submission Date of Structure Product Labeling (SPL): March 23, 2010

Type of Labeling Reviewed: SPL

Background and Summary

This review provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Review

The following issues/deficiencies have been identified in your proposed labeling.

- I. Highlights of Prescribing Information
 - a. The route of administration should be omitted if it is typical for the dosage form and is commonly understood (e.g., tablets or capsules).
 - b. The Revision Date is the Month/Year the application is approved. The revision date should be left blank at the time of application submission.

II. Full Prescribing Information: Contents

- a. The same title for the boxed warning that appears in the Highlights of Prescribing Information and Full Prescribing Information must also appear at the beginning of the Table of Contents in upper-case letters and bold type.
- b. Periods after the section or subsection numbers should not be used.
- c. Identifying numbers must be presented in bold print and must precede the heading or subheading by at least two squares of the size of the letter “m” in 8 point type.

III. Full Prescribing Information

- a. The same title for the boxed warning that appears in the Highlights of Prescribing Information and Table of Contents must also appear at the beginning of the Full Prescribing Information.
- b. Periods after the section or subsection numbers should not be used.
- c. For each contraindication, use numbered subsection headings or bullets.
- d. The Medication Guide or PPI should not be a subsection under the Patient Counseling Information section.
- e. The Patient Counseling Information section must reference any FDA-approved patient labeling (e.g. Medication Guide or Patient Package Insert). [See 21CFR 201.57(c)(18)] The reference “[*see FDA-Approved Patient Labeling* or *See Medication Guide*]” should appear at the beginning of the Patient Counseling Information section.
- f. The statement of the place of business shall include the street address, city, State, and ZIP code. The street address may be omitted if it is shown in a current city directory or telephone directory. [See 21CFR 201.1]
- g. The revision date at the end of the Highlights section replaces the revision date at the end of the labeling. The revision date should not appear in both places.

Recommendations

The RPM will request the sponsor address the identified deficiencies/issues and re-submit labeling by August 5, 2010. This updated version of labeling will be used for further labeling discussions.

Todd Phillips, PharmD
Regulatory Project Manager
Division of Gastroenterology Products

Supervisory Comment/Concurrence:

Wes Ishihara
Chief, Project Management Staff
Division of Gastroenterology Products

Drafted: TDP/29APR2010

Revised/Initialed: WI/13MAY2010

Finalized: TDP/18MAY2010

Filename: CSO Labeling Review Template (updated 1-16-07).doc

CSO LABELING REVIEW OF PLR FORMAT

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22519

ORIG-1

HORIZON PHARMA HZT-501
INC

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

/s/

TODD D PHILLIPS
05/18/2010

RICHARD W ISHIHARA
05/18/2010