

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022535Orig1s000

OTHER REVIEW(S)

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review: August 20, 2014
Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products
Application Type and Number: NDA 022535
Product Name and Strength: Esbriet (Pirfenidone) Capsules, 267 mg
Product Type: Single
Rx or OTC: Rx
Applicant/Sponsor Name: InterMune, Inc.
Submission Date: May 23, 2014
OSE RCM #: 2014-1159
DMEPA Primary Reviewer: Lissa C. Owens, PharmD
DMEPA Team Leader: Kendra Worthy, PharmD
DMEPA Associate Director: Lubna Merchant, M.S., PharmD

1 REASON FOR REVIEW

This review evaluates the proposed container labels and carton labeling, and full prescribing information for the NME Esbriet (Pirfenidone) Capsules for risk of medication error in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). DPARP requested this as part of their evaluation for NDA 022535.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
FDA Adverse Event Reporting System (FAERS)	N/A
Previous DMEPA Reviews	C
Human Factors Study	N/A
ISMP Newsletters	N/A
Other	N/A
Labels and Labeling	G

N/A=not applicable for this review

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Pirfenidone is not currently marketed in the United States. This drug was granted a breakthrough therapy designation on July 17, 2014 for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function.

We performed a risk assessment of the proposed full prescribing information, labels and labeling to identify deficiencies that may lead to medication errors.

In the container labels and carton labeling, we note the presentation of the strength could be improved to provide clarity. Additionally, the presentation of the net quantity could be improved to decrease confusion.

4 CONCLUSION & RECOMMENDATIONS

We conclude that the prescribing information is acceptable. However, the proposed container label and carton labeling can be improved to increase the prominence of important information on the label to promote the safe use of the product. We provide the following recommendations in Section 4.1

4.1 RECOMMENDATIONS FOR INTERMUNE

A. All Container Labels and Carton Labeling

1. [REDACTED] ^{(b) (4)}. The established name presentation should include the active ingredient followed by the dosage form. Include the dosage form *Capsules* on all labels and labeling. Ensure the dosage form presentation is commensurate with the prominence of the active ingredient presentation. Relocate the strength from the bottom of the label and labeling to after the dosage form so that it is easily recognized: see example below

Esbriet
(Pirfenidone) Capsules
267 mg

2. The trade name and established name is listed at the top and bottom of the label and labeling. Consider deleting the presentation at the bottom of the label and labeling as it is redundant information.

B. Carton Labeling and Container Label (270 count bottle)

1. Decrease the prominence of the net quantity (270 Capsules) as it competes for prominence with the strength (267 mg). Since these numbers are numerically similar they may be confused for one another.

C. Titration Blister Labels

1. Add the important identifying information (i.e. trade name, established name, strength) to the blister cards to provide clarity.

D. Titration and Maintenance Dose Pak Labeling

1. Relocate the statements '14 day Titration Pak' on the Titration Pak, and 'Weekly Dosepak' on the Maintenance Dose Pak to above the 'Attention Pharmacist:...'

statement on the principal display panel so that the information is readily available and to help decrease selection errors between the two dosepacks.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Esbriet that InterMune submitted on May 23, 2014.

Table 2. Relevant Product Information for Esbriet	
Initial Approval Date	N/A
Active Ingredient	Pirfenidone
Indication	Treatment of idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function
Route of Administration	Oral
Dosage Form	Capsules
Strength	267 mg
Dose and Frequency	Days 1-7 : (1) 267 mg capsule three times a day with food Days 8-14: (2) 267 mg capsules three times a day with food Days 15 +: (3) 267 mg capsules three times a day with food
How Supplied	Bottles for a 30-day supply, 14-day titration blister pack, or 4-week maintenance blister pack
Storage	25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F)

APPENDIX C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L: Drive on August 15, 2014 using the terms, Esbriet to identify reviews previously performed by DMEPA.

C.2 Results

Our search identified one previous review¹; this was the label and labeling review completed when the labels were originally submitted November 4, 2009. We confirmed that the majority of our previous recommendations were implemented and reiterated any recommendations that should be instituted in section 4.1.

¹ Oleszczuk Z. Label and Labeling Review for Esbriet (NDA 022535). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2010 April 15. 15 p. OSE RCM No.: 2009-2284.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Esbriet labels and labeling submitted by InterMune on May 23, 2014.

- Container label
- Carton labeling
- Full Prescribing Information

G.2 Label and Labeling Images



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² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

LISSA C OWENS
08/20/2014

KENDRA C WORTHY
08/20/2014

LUBNA A MERCHANT
08/20/2014

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

PATIENT LABELING REVIEW

Date: August 20, 2014

To: Badrul Chowdhury, M.D.
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Roberta Szydlo, RPh, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ESBRIET (pirfenidone)

Dosage Form and Route: capsules

Application Type/Number: NDA 22-535

Applicant: InterMune, Inc.

1 INTRODUCTION

On November 4, 2009, InterMune, Inc. submitted for the Agency's review a New Drug Application for pirfenidone capsules. Pirfenidone capsules are indicated for the treatment of idiopathic pulmonary fibrosis (IPF). On May 4, 2010, InterMune was issued a Complete Response Letter by the agency. On May 23, 2014, InterMune, Inc. resubmitted the application to address the issues identified in the Complete Response Letter.

Pirfenidone was granted Orphan Drug Designation on March 5, 2004. The IPF clinical development program also received Fast Track Designation on May 31, 2013, based on the life-threatening nature of the disease and the serious unmet medical need in the U.S.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on June 11, 2014, and June 11, 2014, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for pirfenidone capsules.

2 MATERIAL REVIEWED

- Draft ESBRIET (pirfenidone) PPI received on May 23, 2014, and received by DMPP on August 13, 2014.
- Draft ESBRIET (pirfenidone) PPI received on May 23, 2014, and received by OPDP on August 13, 2014..
- Draft ESBRIET (pirfenidone) Prescribing Information (PI) received on May 23, 2014, revised by the Review Division throughout the review cycle, and received by DMPP on August 13, 2014.
- Draft ESBRIET (pirfenidone) Prescribing Information (PI) received on May 23, 2014, revised by the Review Division throughout the review cycle, and received by OPDP on August 13, 2014.

3 REVIEW METHODS

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 APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Verdana font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
08/20/2014

ROBERTA T SZYDLO
08/20/2014

MELISSA I HULETT
08/20/2014

LASHAWN M GRIFFITHS
08/20/2014

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

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

Memorandum

Date: August 18, 2014

To: Jessica Lee, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Roberta Szydlo, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

cc: Kathleen Klemm, Team Leader, OPDP

Subject: NDA 022535
OPDP labeling comments for Esbriet (pirfenidone) capsules

In response to DPARP's consult request dated June 11, 2014, OPDP has reviewed the proposed draft labeling (Package Insert [PI] and Carton and Container Labeling) for Esbriet (pirfenidone) capsules (Esbriet) and offers the following comments. OPDP's comments on the proposed Patient Package Insert (PPI) will be provided at a later date under separate cover in collaboration with the Division of Medical Policy Programs (DMPP).

OPDP's comments on the PI are provided directly below and are based on the draft marked-up labeling titled "NDA 22535_proposed labeling_5.23.14_BKS_SCPI.docx" that was provided via email from DPARP on August 13, 2014.

OPDP has also reviewed the proposed carton and container labeling submitted by the sponsor on May 23, 2014 (eCTD sequence #0045), and available at:

- <\\cdsesub1\evsprod\nda022535\0045\m1\us\114-label\1141-draft-label\carton-draft-blister-.pdf>
- <\\cdsesub1\evsprod\nda022535\0045\m1\us\114-label\1141-draft-label\carton-draft-bottle.pdf>
- <\\cdsesub1\evsprod\nda022535\0045\m1\us\114-label\1141-draft-label\contain-draft-bottle.pdf>
- <\\cdsesub1\evsprod\nda022535\0045\m1\us\114-label\1141-draft-label\carton-draft-titration-blister.pdf>
- <\\cdsesub1\evsprod\nda022535\0045\m1\us\114-label\1141-draft-label\carton-draft-weekly-blister.pdf>

We have no comments at this time on the proposed carton and container labeling.

Thank you for your consult. OPDP appreciates the opportunity to provide comments on the proposed labeling.

If you have any questions, please contact Roberta Szydlo at (301) 796-5389 or roberta.szydlo@fda.hhs.gov.

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/s/

ROBERTA T SZYDLO
08/18/2014

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

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

Application: NDA 022535

Application Type: Class 2 NDA Resubmission

Name of Drug/Dosage Form: Esbriet (pirfenidone) 267 mg capsules

Applicant: InterMune, Inc.

Receipt Date: 5/23/14

Goal Date: 11/23/14

1. Regulatory History and Applicant's Main Proposals

The Original NDA 22535 was received November 4, 2009. A Complete Response Action was taken on May 4, 2010. Labeling discussions did not occur with the applicant during the first review cycle.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

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

All SRPI format deficiencies of the PI will be conveyed to the applicant in an advice letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by **July 25, 2014**. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

Appendix

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

Highlights

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

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

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

Comment: *HL is longer than 1/2 page*

- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment:

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: *Need white space in sections of DOSAGE FORMS AND STRENGTHS, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS*

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

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

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

Selected Requirements of Prescribing Information

• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)
• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

Comment:

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

Selected Requirements of Prescribing Information

Comment:

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

YES

Selected Requirements of Prescribing Information

21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

Comment:

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

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

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

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6 ADVERSE REACTIONS

6.1 [text]

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7 DRUG INTERACTIONS

7.1 [text]

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8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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9 DRUG ABUSE AND DEPENDENCE

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12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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14 CLINICAL STUDIES

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15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

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/s/

JESSICA K LEE
07/08/2014

LADAN JAFARI
07/08/2014



**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: April 15, 2010

To: Badrul Chowdhury, M.D., Ph.D., Director
Division of Pulmonary, Allergy, and Rheumatology Products

Through: Denise Toyer, PharmD, Deputy Director
Division of Medication Error Prevention and Analysis

From: Zachary Oleszczuk, PharmD, Acting Team Leader
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Esbriet (Pirfenidone) Capsules
267 mg

Application Type/Number: NDA 022535

Applicant: InterMune, Inc.

OSE RCM #: 2009-2284

1 INTRODUCTION

This review is written in response to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPAAP) for assessment of the container labels, carton labeling, insert labeling, medication guide labeling, titration blister labels, titration pack labeling, maintenance blister labels, and maintenance package labeling.

1.1 REGULATORY HISTORY

NDA 022535 for Esbriet was submitted on November 4, 2009. It has been granted orphan designation.

2 METHODS AND MATERIALS

2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) DATABASE

Since, the active ingredient pirfenidone is currently marketed in foreign countries under the proprietary name Pirespa, DMEPA conducted a search of the Adverse Event Reporting System (AERS) on March 8, 2010 using the active ingredient name “pirfenidone” and the verbatim terms “Pires%” and “pirfe%” along with the MedDRA reaction terms “Medication Errors” (HLGT), “Product Quality Issue” (PT) and “Product Label Issue” (HLT). The tradename ‘Esbriet’ was not used as a proprietary name because the name does not appear as a tradename in the AERS drug database.

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

Our search of the Adverse event database did not identify any cases of medication errors reports involving pirfenidone. However, since medication errors are known to be under reported and this product is currently marketed in foreign markets only, a negative AERS result can not guarantee that errors are not occurring, only that the errors are not being reported to the FDA.

2.2 LABELS AND LABELING

The Applicant submitted a Risk Evaluation Minimization Strategy that included a restricted distribution plan (no image) and medication guide labeling (no image) for Esbriet (pirfenidone) Capsules on November 4, 2009. The Applicant also submitted insert labeling (no image) on April 8, 2010. Additionally, the Applicant submitted container labels (see Appendix A), carton labeling (see Appendix B), titration pack blister labels (see Appendix C), titration pack carton labeling (see Appendix D), maintenance package blister labels (see Appendix E), maintenance package carton labeling (see Appendix F), and maintenance package out carton labeling (see Appendix G) on April 5, 2010. DMEPA used Failure Mode and Effects Analysis (FMEA)¹ in our evaluation of the labels, labeling, and packaging configuration.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

3 CONCLUSIONS AND RECOMMENDATIONS

Our evaluation of the labels and labeling noted areas where the presentation of information can be improved to minimize the potential for medication errors. We provide our recommendations for the package insert labeling and Medication Guide labeling in Section 3.1, *Comments to the Division*. Section 3.2, *Comments to the Applicant* contains our recommendations for the container labels and 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 questions or need clarifications, please contact Carolyn Volpe, OSE Regulatory Project manager, at 301-796-5204.

3.1 COMMENTS TO THE DIVISION

3.1.1 Package Insert

1. We note that the symbol ‘x’ is used to represent the word ‘times’ through out the package insert labeling. Symbols can cause confusion and lead to medication error if they are misinterpreted. We recommend revising the package insert to replace all instances of ‘x’ with the word ‘times’.
2. We note the abbreviation ‘IPF’ is used to represent Idiopathic Pulmonary Fibrosis. The abbreviations ‘IPF’ has several meaning² such as: Ibuprofen, Immune Protection Factor, Infection Potentiating Factor, Inhibitory Protein Factor, and Insulin Promoter Factor. Since the abbreviation ‘IPF’ has several meanings and can be misinterpreted we recommend removing all instances of the abbreviation ‘IPF’ and replacing the abbreviation with the statement ‘Idiopathic Pulmonary Fibrosis’ where appropriate.
3. Section 2.1, *Dosage and Administration* can be reorganized to be to help clarify the dosing instruction. As presented now the maintenance daily dose is presented before the titration schedule. Since this drug should be titrated when first started the instructions for titration should be presented before the maintenance dose.

Reorder the presentation of information so the instructions for titration appear before the instructions for maintenance dose as follow:

When first prescribed, Esbriet therapy should be titrated over two weeks as follows:

Table 1. Dose Escalation for TRADENAME

Treatment Days	Dose
Days 1 through 7	1 capsule three times a day with meals
Days 8 through 14	2 capsules three times a day with meals
Days 15 and above	3 capsules three times a day with meals

² Medilexicon;

<http://www.medilexicon.com/medicalabbreviations.php?keywords=IPF&search=abbreviation;>

March 12, 2010

The recommended daily maintenance dosage of Esbriet for treatment of patients with Idiopathic Pulmonary Fibrosis is three 267 mg capsules three times a day with food for a total of 2403 mg/day.

Doses above 2403 mg/day are not recommended for any patient.

3.1.2 Medication Guide Labeling

We have provided the following comments on the Medication Guide to the Division of Risk Management:

1. We note the abbreviation 'IPF' is used to represent Idiopathic Pulmonary Fibrosis. The abbreviations 'IPF' has several meaning³ such as: Ibuprofen, Immune Protection Factor, Infection Potentiating Factor, Inhibitory Protein Factor, and Insulin Promoter Factor. Additionally, patients may not understand the abbreviation 'IPF'. Since the abbreviation 'IPF' has several meanings, can be misinterpreted, and may not be understood by patients, we recommend removing all instances of the abbreviation 'IPF'.
2. The dosing instructions in the second bullet of the section "How should I take TRADENAME" are confusing and can be revised to be easier to understand. Revise the dosing instruction in the second bullet as follows:



3. The dosing instructions in the third bullet of the section "How should I take TRADENAME" can be revised to be easier to understand. Revise the dosing instruction in the third bullet as follows:



³ Medilexicon;

<http://www.medilexicon.com/medicalabbreviations.php?keywords=IPF&search=abbreviation;>

March 12, 2010

3.2 COMMENTS TO THE APPLICANT

A. GENERAL COMMENT

1. To be consistent with other currently marketed capsules capitalize the ‘c’ in the word capsules that immediately follows established name and remove the comma separating the dosage form from and strength.

Esbriet
(pirfenidone)
Capsules 267 mg

B. CONTAINER LABELS

1. Include the statement “Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily” on the side panel to help minimize the risk of exposure to sunlight.
2. To comply with 21 CFR 201.25, revise the labels to include a bar code.
3. Increase the prominence of the statement (b) (4)

C. CARTON LABELING

1. Increase the prominence of the statement (b) (4)
2. Include the statement “Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily” on the side panel to help minimize the risk of exposure to sunlight.
3. The net quantity (270 Capsules) is bolded and competes with prominence with the strength (267 mg). Since these numbers are numerically similar they may be confused for one another. Decrease the prominence of the net quantity (270 CAPSULES) by using font that is not bolded.

E. TITRATION PACK BLISTER LABELS

1. The abbreviations used to describe the time of day (AM, Noon, and PM) a patient is scheduled to take their medication can be improved to enhance the message that this medication should be taken with food to decrease the risk of adverse events. Revise the abbreviations “AM”, “Noon”, and “PM” to the appropriate meal at that time of day such as “Breakfast”, “Lunch”, and “Dinner”.
2. To make the dosing instructions easier to locate include them on the blister card as well as the carton. The dosing instructions should be located immediately following the week dosing and should be presented as follows:

Week 1 Dosing – Take 1 capsule orally three times a day with meals

Week 2 Dosing – Take 2 capsules orally three times a day with meals

3. The number of days located on the bottom of the blister card may be overlooked by patients. Revise the number of days to be presented on the top of the blister card for the corresponding day. The Days should be located directly underneath the week dosing comment and presented as follows:

Week 1 Dosing – [REDACTED] (b) (4)
Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7

or

Week 2 Dosing – [REDACTED] (b) (4)
Day 8 Day 9 Day 10 Day 11 Day 12 Day 13 Day 14

F. TITRATION PACK CARTON LABELING

1. Increase the prominence of the statement [REDACTED] (b) (4)
[REDACTED]
2. Include a total net quantity (63 Capsules) statement on the principal display panel that does not compete for prominence with the strength and revise the net quantity statement on the inside panel to include the total net quantity (63 Capsules). The net quantity statement should appear as follows:

14 Day Titration Dosepak contains 63 Capsules:
Week 1 Dosing contains 21 capsules
Week 2 Dosing contains 42 capsules

3. Include the statement “Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily” on the principal display panel to help minimize the risk of exposure to sunlight.
4. The carton labeling for the Titration Pack and the Maintenance Pack appear similar. Use color differentiation to help differentiate the two packs. Additionally, revise the principal display panel to included the specific dosing instruction for titration to help differentiate the two packs and to clearly identify the titration instructions. The titration schedule should be presented as follows:

Days 1 through 7: Take one capsule orally three times a day with meals
Days 8 through 14: Take two capsules orally three times a day with meals

G. MAINTENANCE PACK BLISTER LABELS

1. The abbreviations used to describe the time of day (AM, Noon, and PM) a patient is scheduled to take their medication can be improved to enhance the message that this medication should be taken with food to decrease the risk of adverse events. Revise the abbreviations “AM”, “Noon”, and “PM” to the appropriate meal at that time of day such as “Breakfast”, “Lunch”, and “Dinner” on the container labels and carton labeling.
2. To make the dosing instructions easier to locate include them on the blister card as well as the carton. The dosing instructions should be located immediately above the blisters and should be presented as follows:

[REDACTED] (b) (4)

3. The number of days located on the bottom of the blister card may be overlooked by patients. Revise the number of days to be presented on the top of the blister card for the corresponding day. The Days should be located directly underneath the week dosing comment and presented as follows:

(b) (4)

Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7

4. The dose associated with each time of day (AM, Noon, and PM) are not well defined and may confuse patients. Patients may assume that they are only supposed to take the capsules that are directly across from the time of day.

(b) (4)

(b) (4)

H. MAINTENANCE PACK CARTON LABELING

1. Increase the prominence of the statement (b) (4)
2. Include the statement “Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily” on the principal display panel to help minimize the risk of exposure to sunlight.
3. Increase the prominence of the strength on the principal display panel.
4. The carton labeling for the Titration Pack and the Maintenance Pack appear similar particularly if the (b) (4) is removed from the outer carton. Revise the color of the (b) (4) to be dissimilar from the color of the carton for the Titration pack and to also be dissimilar to the outer carton of the Maintenance pack. To further help differentiate the two packs Include the word ‘Maintenance’ in the statement (b) (4) The revised statement should appear as follows:

(b) (4)

I. MAINTENANCE PACK OUTER CARTON LABELING

1. Increase the prominence of the statement (b) (4)

 to alert pharmacists that this medication should be dispensed with a medication guide.
2. The net quantity statement is confusing. Revise the net quantity to be easier to understand. The net quantity statement should appear as follows:
3. Include the statement “Avoid exposure to sunlight and sunlamps. Wear sunscreen and protective clothing daily” on the principal display panel to help minimize the risk of exposure to sunlight.

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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

ZACHARY A OLESZCZUK
04/15/2010

DENISE P TOYER
04/15/2010

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: April 2, 2010

TO: Eunice Chung, PharmD, Regulatory Project Manager
Banu Karimi-Shah, M.D., Medical Officer
Division of Pulmonary, Allergy and Rheumatologic Products

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

FROM: Anthony Orenca, MD, FACP
Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 22-535

APPLICANT: InterMune

DRUG: pirfenidone (Esbriet) capsule

THERAPEUTIC CLASSIFICATION: Priority Review

INDICATIONS: treatment of idiopathic pulmonary fibrosis (IPF)

CONSULTATION REQUEST DATE: January 13, 2010

DIVISION ACTION GOAL DATE: May 4, 2010

PDUFA DATE: May 4, 2010

I. BACKGROUND:

Idiopathic Pulmonary Fibrosis (IPF) is a disease of unknown etiology with progressive pulmonary insufficiency, and characterized, pathophysiologically, as interstitial fibrosis of the lung and decrease in lung volume. The reported estimated median survival after diagnosis is 2.5 to 3.5 years.

Pirfenidone is an antifibrotic and anti-inflammatory agent being developed for IPF. The mechanism of action of pirfenidone, a small nonpeptide molecule, has not been fully established. While no drugs are approved for the treatment of IPF in the U.S., one product is approved internationally for the treatment of IPF; on October 16, 2008, the Japanese Ministry of Health approved pirfenidone tablets (Pirespa® 200-mg tablet, Shionogi & Co., Ltd.) for the treatment of patients with IPF in Japan.

Open-label and Phase 2 clinical experience with pirfenidone in the USA, Europe, and Japan indicated that doses of 1800 mg/d to 3600 mg/d can be safely administered as a capsule or a tablet. At the doses tested, the most common adverse events were mild to moderate gastrointestinal discomfort, photosensitivity rash, and fatigue. Phase 3 clinical experience with pirfenidone in Japan in randomized, double-blind safety (1200 mg/d and 1800 mg/d) and efficacy (1800 mg/d) studies indicated that the most common adverse events reported in this study were photosensitivity, nasopharyngitis, and anorexia.

Pirfenidone was designated a priority review as a New Molecular Entity (NME). Protocol PIPF-004 was selected for inspection since this study met the primary efficacy endpoint.

Protocol PIPF-004:

PIPF-004 was a Phase 3, randomized, double-blind, placebo-controlled, 3-arm, safety and efficacy study evaluating pirfenidone in 435 patients with IPF at 2403 mg/d of pirfenidone (n = 174) or 1197 mg/d of pirfenidone (n = 87) compared with placebo (n = 174). The objectives of the study were: (a) To assess the safety and efficacy of treatment with pirfenidone 2403 mg/d compared with placebo in patients with IPF, (b) To assess the safety and efficacy of treatment with pirfenidone 1197 mg/d in patients with IPF, and (c) To characterize the pharmacokinetic disposition of pirfenidone in patients with IPF.

Patients aged 40–81 years, who had a confident clinical, radiographic, and/or pathologic diagnosis of IPF without evidence or suspicion of an alternative diagnosis for interstitial lung disease, and who had evidence of disease progression were eligible to participate in the study. The primary efficacy outcome variable was absolute change in percent predicted forced vital capacity (FVC) from baseline to Week 72.

The study covered periods July 14, 2006 thru November 7, 2008. Study PIPF-004 was conducted by 64 investigators at 64 sites in United States, Canada, Mexico, United Kingdom, France, Italy, Poland, and Australia.

Three clinical investigators and the sponsor were selected for inspection. The investigative drug in this application is a new molecular entity (NME) for an indication which currently has no FDA-approved therapies. Clinical sites (see below) were chosen based upon those with highest enrollments, and sites whose results favored the active treatment arm of the trial. The sponsor was selected for inspection as the product is an NME.

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol (s)	Inspection Date	EIR Received Date	Final Classification
Steven P. Nathan, MD/Site #1008	Falls Church, VA	PIPF-004	February 22-24, 2010	March 29, 2010	NAI
James N. Allen, MD /#1016	Columbus, OH	PIPF-004	February 8 – March 1, 2010	Pending	Pending Preliminary field classification: VAI
Jeffrey A. Golden, MD /Site #1015	San Francisco, CA	PIPF-004	February 11-19, 2010	Pending	Pending Preliminary field classification: VAI
InterMune, Inc	Brisbane, CA	Sponsor	February 9 – 24, 2010	March 18, 2010	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Pending= The EIR has not been received and findings are based on preliminary communication with the field.

PROTOCOL PIPF-004

1. Steven P. Nathan, MD/Site #1008

3300 Gallows Road
 Falls Church, VA 22042

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from February 22 to 24, 2010. There were 20 subjects screened, 10 subjects were enrolled, and 7 subjects completed the study. A total of 10 study subject records were reviewed. There was no evidence of under-reporting adverse events. No discrepancies between the source record and the case report form (CRF) were found. Patients were properly consented. Study drug accountability logs were documented.

b. Limitations of inspection:

None.

c. General observations/commentary:

No Form FDA 483 was issued. This clinical site appeared to adhere to good clinical practice. Current inspection showed no discrepancies with source data. There were two reported deaths due to worsening or disease progression, which were verified in the data listings.

d. Data acceptability/reliability for consideration in the NDA review decision:

The data in support of clinical efficacy and safety at this clinical site appear acceptable.

2. James Allen, MD/Site #1016

Ohio Sate University Medical Center
1492 East Broad Street
Columbus, OH 43205

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from February 8 to March 1, 2010.

A total of 27 subjects were screened; 18 subjects were enrolled and randomized, and 14 subjects completed the study. A total of 18 study subject records were reviewed during this site inspection.

The inspection evaluated the following: data collection, data reporting, consent forms, data and source document components, and investigational product accountability.

b. Limitations of inspection:

None.

c. General observations/commentary:

ORA field office classified this clinical site inspection as VAI, and a two-observation Form FDA 483 was issued, for deficiencies in preparing or maintaining accurate case histories with respect to observations pertinent to the investigation, and in conducting a clinical investigation in accordance with the investigational plan. Dr. Allen submitted a response to the Form 483 that DSI received on March 8, 2010, outlining his plan for corrective action regarding the field investigator's findings.

Examples of inspectional findings include the following observations:

- For Subject #4038, per Module 2 (Week 13 to 24) Study Drug Accountability CRF, the number of capsules returned from Week 13 to 24 (4/30/2007) was 900; however, the Subject Compliance Worksheet for this visit (4/13/2007) recorded the total # capsules returned was 109;
- For Subject #4072, per Module 1 (Day 1to Week 12) Study Drug Accountability CRF, the number of capsules returned from Day 1 to Week 12 (4/13/2007) was

- 900; however, the Subject Compliance Worksheet for this visit recorded the total # capsules returned was 126;
- For Subject #4089, according to Module 1 (Day 1 to Week 12) Study Drug Accountability CRF, the number of capsules returned from Day 1 to Week 12 was 900; however, the Subject Compliance Worksheet for this visit (4/25/2007) recorded the total # capsules returned was 219;
 - For Subject #4014, per Treatment Completion Study Drug Accountability CRF, the number of capsules returned at this visit (9/2/2008) was 411; however, the Subject Compliance Worksheet (Day 1-Treatment Completion) recorded the total # capsules returned at this visit as 309;
 - For Subject #4007, per Screening (8/2/2006) in the Oxygen Titration Procedure CRF, the patient reported a Post-walk Borg Scale rating of moderate; however, the source document recorded a rating of slight;
 - For Subject #4023, per Week 12 (12/15/2006) Routine Clinical ECG CRF, the Bazett's rate-corrected QT interval was greater than 500 milliseconds; however, the source document recorded the interval as 420 milliseconds;
 - Subject #4023 recorded (11/10/2006) in the patient screening to week 12 diary that she had progressively worsening cough; however, this was not reported in the sponsor's Adverse Events CRF.

Reviewer's Comments: Regarding the aforementioned Study Drug Accountability CRF deficiency findings, these were mainly transcription errors, as discussed with the district office field investigator in a teleconference on April 6, 2010. The field investigator was able to verify and confirm accuracy and completeness of study drug accountability from source documents.

The study drug was dispensed according to protocol and subjects received the investigational product to which they were randomized. There were no instances where the blind was broken. The source documents for the number of capsules returned and dispensed were accurately calculated, appropriately reconciled, and recorded. Dr. Allen's staff, however, recorded the number of capsules dispensed instead of total number of capsules returned. With the exception of transcription errors as noted above, there were no systemic or pervasive problems with test article accountability. In general, there were no issues identified during the clinical inspection that would suggest that the data integrity was compromised.

Dr. Allen acknowledged these transcription errors in his letter response. As part of his corrective action plan, he plans to develop an internal audit process, with regular frequency, by peers to prevent documentation errors.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

d. Data acceptability/reliability for consideration in the NDA review decision:

While some regulatory violations were observed, these are unlikely to importantly impact data integrity. The data in support of clinical efficacy and safety from this clinical site appear acceptable.

3. Jeffrey A. Golden, MD/Site #1015

Box 0359, Room A-540
400 Parnassus Avenue
San Francisco, CA 94143-0359

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.811, from February 11 to 19, 2010.

A total of 22 subjects were screened at this clinical site; 17 subjects were enrolled and randomized. There were 17 subject records inspected for informed consent, primary efficacy endpoint data, and 5 patient records inspected for patient diaries and for other potential discrepancies between source documents and CRFs. No evidence of under-reporting of adverse events was noted.

The inspection also evaluated the following: data collection, data reporting, IRB approvals, data and source document components, and investigational product accountability.

b. Limitations of inspection:

None.

c. General observations/commentary:

ORA field office classified this clinical site inspection as VAI, and a three-observation Form FDA 483 was issued, for deficiencies in preparing or maintaining accurate case histories with respect to observations pertinent to the investigation, and in failure to obtain informed consent in accordance with 21 CFR Part 50 prior to conducting the study, as well as implementing research activities despite lack of approval to all changes by the Institutional Review Board. Dr. Golden issued a response to the Form 483 that DSI received a response on March 11, 2010, outlining his plan for corrective action regarding the field investigator's findings. Dr. Golden submitted source documents on investigational product accountability and pulmonary function test worksheets, and stated that his team reorganized patient subject binders, and upon further review, Dr. Golden appear to have maintained accurate case histories in his clinical study.

Specific minor regulatory deficiencies included the following:

- Informed consent forms, updated version August 11, 2008, were not obtained for subjects 1015 4238, 1015 4255 and 1015 4129.
- The informed consent form, version June 27, 2008, was not submitted to the Institutional Review Board prior to study implementation on the research subjects.

d. Data acceptability/reliability for consideration in the NDA review decision:

While minor deficiencies were observed for PIPF-004 , these observations do not appear to have a substantive impact on data integrity and patient safety. The data in support of clinical efficacy and safety from this clinical site appear acceptable.

NOTE: Observations noted above are based on preliminary communications with the field investigator, and an inspection summary addendum will be generated if conclusions change upon review and receipt of the EIR.

4. InterMune/Sponsor

3260 Bayshore Boulevard
Brisbane, Ca 94005

a. What was inspected?

The inspection was conducted in accordance with Compliance Program 7348.810 from February 9 to 24, 2010. The inspection evaluated the following documents: structural organization, clinical study sites, selection of clinical investigators (i.e., only pulmonologists participated as clinical investigators), and master services agreements. InterMune contracted with (b) (4) to monitor the clinical sites, except for the following clinical sites performed by InterMune: Dr. Jeffrey Golden (Site 1015), Dr. David Zisman (Site 1016), and Dr. Andrew Chan (Site 1002). Clinical trial monitoring included the following: project management, site visits every four to five weeks, site protocol compliance, review of case report forms and informed consent forms, drug accountability, adequate reporting assessment of adverse events, and review of source data..

b. Limitations of inspection:

None.

c. General observations/commentary:

A two-observation Form FDA 483 was issued on February 24, 2010 at the end of the inspection for lacking to ensure proper monitoring of the study (21 CFR 312.50) and for lack of detailed descriptions of obligations in the full or partial transfer of obligations to a contract research organization (e.g., (b) (4) (21 CFR 312.52(b)), albeit no substantive regulatory violations were noted in Protocol PIPF-004. Sponsor provided a written response on March 5, 2010 for the firm's corrective action plans to the ORA San Francisco District Office. that was received on March 8, 2010.

For example:

- Site 1002 needed training on obtaining a proper informed consent as documented on sponsor's site monitoring visit dated June 9, 2008, but a corrective action plan was not developed to prevent recurrence of this deficiency,

- CRO agreement misrepresented that (b) (4) shall conduct serious adverse event and patient eligibility monitoring, where the sponsor fully reviewed and evaluated these.

d. Data acceptability/reliability for consideration in the NDA review decision:

While minor regulatory observations were noted, these do not appear to have a significant impact on data integrity and patient safety of these clinical trials. The data in support of clinical efficacy and safety at this clinical site appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Three domestic clinical investigator sites and the sponsor were inspected in support of this application for study Protocol PIPF-004, in support of pirfenidone for the treatment of idiopathic pulmonary fibrosis.

In general, inspection findings documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. Although minor regulatory violations were noted, these are isolated in nature, and are unlikely to impact data integrity and patient safety. The data generated by these inspected sites appear reliable in support of the application.

Note: Observations noted above for these three clinical sites are based on the Form FDA 483, preliminary EIR and communications from field investigator, an inspection summary addendum will be generated if conclusions change significantly upon receipt and review of the final EIR.

{See appended electronic signature page}

Anthony Orenca, M.D.
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

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

ANTHONY J ORENCIA
04/06/2010

TEJASHRI S PUROHIT-SHETH
04/07/2010

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

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

Memorandum

Date: April 5, 2010

To: Eunice H. Chung, Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

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

Through: Sam Skariah, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications
(DDMAC)

CC: Robyn Tyler, Regulatory Review Officer
Lisa Hubbard, Professional Group Leader
Sangeeta Vaswani, DTC Group Leader
Wayne Amchin, Regulatory Health Project Manager
DDMAC

Subject: NDA # 022535
DDMAC labeling comments for Esbriet (pirfenidone) Capsules

DDMAC has reviewed the proposed product labeling (PI) for Esbriet (pirfenidone) Capsules (Esbriet) submitted for consult on December 15, 2009. DDMAC's comments are based on the proposed draft marked-up labeling titled "Pirfenidone_Label_edited.doc" that was sent via email from DPARP to DDMAC on April 5, 2010.

DDMAC's comments on the PI are provided directly in the marked-up document attached (see below). DDMAC's comments regarding the Medication Guide will be sent at a later date under separate cover after DPARP forwards the draft document to DDMAC for review.

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

If you have any questions regarding the PI, please contact Roberta Szydlo at (301) 796-5389 or Roberta.szydlo@fda.hhs.gov.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

ROBERTA T SZYDLO
04/05/2010

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-535
APPLICANT	InterMune, Inc.
DRUG NAME	ESBRIET (pirfenidone)
SUBMISSION DATE	November 4, 2009
SEALD REVIEW DATE	March 31, 2010
SEALD REVIEWER(S)	Jeanne M. Delasko, RN, MS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

JEANNE M DELASKO
04/01/2010

LAURIE B BURKE
04/01/2010

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Pulmonary and Allergy Products

Application Number: 22-535

Name of Drug: Esbriet (proposed) pirfenidone

Applicant: InterMune

Material Reviewed:

Submission Date(s): November 4, 2009

Receipt Date(s): November 4, 2009

Submission Date of Structure Product Labeling (SPL): November 4, 2009

Type of Labeling Reviewed: PDF

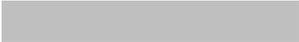
Background and Summary

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 with regard to format:

Highlights Section:

1. In the Contraindications Section,  (b) (4)

2. In the Adverse Reactions Section, add arthralgia as one of the adverse reactions that occur in patients >10%.

3. In the Drug Interactions Section, consider the inclusion of practical instructions for preventing or decreasing the likelihood of the interaction.
4. For the Revision date, remove the parentheses for the month/year.

Full Prescribing Information: Contents

1. Remove periods after the numbers for the section and subsection headings.
2. Omit [REDACTED] (b) (4)

Full Prescribing Information (FPI)

1. The headings and sub headings should be in boldface font for Sections 1 Indications and Usage and 2 Dosage and Administration. Also, remove the periods after the numbers for these sections.
2. For Section 12.3 and Section [REDACTED] (b) (4), all non-heading and non-subheading words (i.e. Absorption, Distribution, Metabolism, Elimination, Geriatric, Gender, Obesity, Race, Hepatic, Renal Impairment, [REDACTED] (b) (4) and Tables and Figures must be normal font. Please change all italics and bold print to normal font.
3. In the Dosage and Administration Section, “TID” should be written out to “three times a day” or other variation.
4. Change “ULN” to “upper limit of normal” globally in the FPI.
5. Omit [REDACTED] (b) (4)

Recommendations

Please address the identified issues and re-submit labeling by January 16, 2010. This updated version of labeling will be used for further labeling discussions.

Eunice H. Chung, Pharm.D.
Regulatory Management Officer

Supervisory Comment/Concurrence:

Sandy Barnes
Chief, Project Management Staff

Drafted: EChung/December 15, 2009

Revised/Initialed: SBarnes/December 31, 2009

Finalized: EChung/December 31, 2009

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-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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/s/

EUNICE H CHUNG
12/31/2009

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 # 22-535 BLA#	NDA Supplement #:S- BLA STN #	Efficacy Supplement Type SE-
Proprietary Name: Esbriet (proposed) Established/Proper Name: pirfenidone Dosage Form: capsules Strengths: 267 mg		
Applicant: InterMune Agent for Applicant (if applicable):		
Date of Application: November 4, 2009 Date of Receipt: November 4, 2009 Date clock started after UN: N/A		
PDUFA Goal Date: May 4, 2010		Action Goal Date (if different):
Filing Date: January 3, 2010		Date of Filing Meeting: December 9, 2009
Chemical Classification: (1,2,3 etc.) (original NDAs only) 1 (NME)		
Proposed indication(s)/Proposed change(s): treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input 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: <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>		<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted
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 checked="" type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:		<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)

Collaborative Review Division (if OTC product):				
List referenced IND Number(s): 67, 284				
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			They do need to submit a proprietary trade name
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 checked="" type="checkbox"/> Exempt (orphan, government) <input 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 checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<i>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).</i>				

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?																				
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)).																				
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>																				
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 If yes, please list below:																				
<table border="1"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> <tr><td> </td><td> </td><td> </td><td> </td></tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<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		There are several compounds that have orphan designation but are not approved with the orphan indication																
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: 7 <i>Note: An applicant can receive exclusivity without requesting it;</i>	X																			

<i>therefore, requesting exclusivity is not required.</i>				
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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 type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.				Sponsor is checking on some links
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			The sponsor included even though this is an electronic submission

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		They have requested a full waiver because this condition does not occur in children. I have asked the PeRC PM and he has stated that orphan drugs are exempt and they do not trigger PREA.
<p>If the application triggers PREA, are the required pediatric assessment studies or a full waiver of pediatric studies included?</p>	X			Full Waiver
<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	
<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			
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 checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request 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>			X	
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 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>				

Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): Finalized 3/05/2005 (Meeting Date: 12/14/2004) <i>If yes, distribute minutes before filing meeting</i>	X			
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): Finalized 9/29/2008 (Meeting Date: 9/17/2008) <i>If yes, distribute minutes before filing meeting</i>	X			
Any Special Protocol Assessments (SPAs)? Date(s): <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: December 9, 2009

BLA/NDA/Supp #: NDA 22-535

PROPRIETARY NAME: Esbriet (proposed)

ESTABLISHED/PROPER NAME: pirfenidone

DOSAGE FORM/STRENGTH: 267 mg capsules

APPLICANT: InterMune

PROPOSED INDICATION(S)/PROPOSED CHANGE(S): The treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function

BACKGROUND: This drug was previously studied in IND 67, 284. The IND was given orphan drug designation status. The sponsor is submitting their NDA and is requesting a priority review (6 month clock).

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Eunice Chung	Y
	CPMS/TL:	Sandy Barnes	N
Cross-Discipline Team Leader (CDTL)	Sally Seymour		Y
Clinical	Reviewer:	Banu Karimi Shah	Y
	TL:	Sally Seymour	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:		

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Clinical Pharmacology	Reviewer:	Elizabeth Yili Shang	Y
	TL:	Partha Roy	Y
Biostatistics	Reviewer:	Feng Zhou	Y
	TL:	Tom Permutt	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Timothy Robison	Y
	TL:	Luqi Pei	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:		
	TL:		
Product Quality (CMC)	Reviewer:	Xiaobin Shen	Y
	TL:	Prasad Peri	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:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Tara Turner	Y
	TL:	Zach Oleszczuk	N
OSE/DRISK (REMS)	Reviewer:	Shawna Hutchins	
	TL:	LaShawn Griffiths	N
Bioresearch Monitoring (DSI)	Reviewer:	Anthony Orenca	Y
	TL:		

Other reviewers	Alan Schroeder	Y
Other attendees	Curtis Rosebraugh, Lee Ripper, Jean Mulinde,	Y

FILING MEETING DISCUSSION:

GENERAL	
<ul style="list-style-type: none"> 505(b)(2) filing issues? <p>If yes, list issues: See Clinical and Statistical Filing Reviews regarding Primary efficacy variables</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input 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
CLINICAL	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE
<p>Comments: There were a few potential refuse to file issues but they have been worked out with upper management</p>	<input checked="" 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</i> 	<input checked="" type="checkbox"/> YES Date if known: March 9, 2010 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:

<i>disease</i>	
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<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 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 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: Curtis Rosebraugh	
21st Century Review Milestones (see attached) (optional):	
Comments:	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input 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 type="checkbox"/> Standard Review <input checked="" type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input checked="" 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 checked="" 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 type="checkbox"/>	Send review issues/no review issues by day 74. Pending for January 17, 2010
<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-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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

/s/

EUNICE H CHUNG
12/31/2009