

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022535Orig1s000

CHEMISTRY REVIEW(S)

NDA 22-535

Esbriet Pirfenidone Capsules, 267 mg

ONDQA Division Director Review

InterMune, Inc.

Chemistry, Manufacturing, and Controls Division Director's Summary Basis of Action

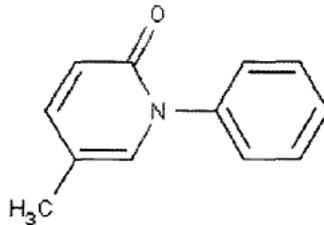
Applicant: InterMune, Inc.
3280 Bayshore Blvd
Brisbane CA

Indication: Treatment of idiopathic pulmonary fibrosis

EER Status:

The Office of Compliance issued an overall recommendation of ACCEPTABLE for the application on 16-JUN-2014

Drug Substance:



Drug substance is manufactured in (b) (4) see below.

No polymorphs have been detected. Specifications are considered acceptable. Drug substance retest period is (b) (4) months.

Drug Substance: Satisfactory

Drug Product:

Drug product is a white/white capsule prepared by (b) (4)

Presentations: The capsules are supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card contains 21, 42 or 63 capsules per blister card.

Specifications are considered acceptable. Stability data support a 48 month expiry in all presentations.

Drug Product: Satisfactory.

Labeling:

Container and carton labels and package insert are acceptable.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval.

Eric P. Duffy -S

Digitally signed by Eric P. Duffy -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Eric P. Duffy -S,
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Date: 2014.10.08 16:02:38 -04'00'

NDA 22-535

Pirfenidone Capsule

InterMune, Inc.

Xiaobin Shen, Ph.D.

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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Chemistry Review Data Sheet

1. NDA 22-535
2. REVIEW #: 3 Amendment
3. REVIEW DATE: 12-Sep-2014
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	04-Nov-2009
Amendment 0015	29-Jan-2010
Amendment 0018	12-Feb-2010
Amendment 0028	05-Mar-2010
Amendment 0031	18-Mar-2010
Amendment 0033	25-Mar-2010
Amendment 0034	25-Mar-2010
Amendment 0035	06-Apr-2010

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0045	23-May-2014
Amendment 0049	04-Aug-2014

Other amendments not listed do not have CMC information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: InterMune, Inc.

Chemistry Review Data Sheet

Address: 3280 Bayshore Boulevard
Brisbane, CA 94005

Representative: Marianne Armstrong, Ph.D.

Telephone: 415-840-4831

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Esbriet
- b) Non-Proprietary Name (USAN): Pirfenidone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: Not established

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 267 mg/capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

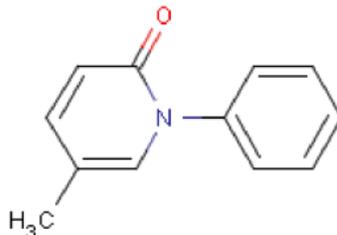
Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

5-methyl-1-phenyl-2-(1H)-pyridone;

(b) (4)

Molecular formula: C₁₂H₁₁NO

Molecular Weight: 185.23 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Adequate	05-Aug-2014	
	IV			4		NA	
	III			4		NA	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	

Chemistry Review Data Sheet

(b) (4)	III	(b) (4)	4	N/A	
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,284	Pirfenidone 400 mg capsule

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	11-Sep-2014	Dr. Ruth Moore
Pharm/Tox	Approval	13-Aug-2014	Dr. Timothy W. Robison
Biopharm	Not needed	NA	NA
Methods Validation	Not needed	NA	NA
EA	Adequate	30-Jul-2014	Dr. Xiaobin Shen
Microbiology	Approval	14-Aug-2014	Dr. Robert Mello

The Chemistry Review for NDA 22-535

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Products

Drug substance pirfenidone is developed as a treatment for patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Its pharmacological category has not been established. Pirfenidone is a small synthetic non-peptide new molecular entity. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. Pirfenidone does not possess polymorphism.

Pirfenidone is prepared through (b) (4)

(b) (4). Specifications for the starting materials, reagents, and in-process control are adequate. The structure of pirfenidone was confirmed by a combination of the spectroscopic and analytic techniques. Specifications for pirfenidone drug substance include appearance, identification, assay, related substances, water content, residue on ignition, heavy metals, loss on drying and particle size distribution. The support of drug substance is referenced to DMF (b) (4) which has been deemed adequate by this reviewer on 05-Aug-2014. The drug substance retest period is (b) (4) months. The drug substance manufacturing site has an acceptable EES status as of 11-Sep-2014.

The drug product is manufactured as size 1 capsules. Each contains 267 mg pirfenidone. There are two presentations. The white body and white cap capsules are to be marketed in the United States. The blue body and gold cap capsules are to be marketed in Europe and Canada. The two presentations (b) (4). The excipients used include croscarmellose sodium, microcrystalline cellulose, povidone, and magnesium stearate. The capsules are supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card can contain 21, 42 or 63 capsules per blister card. The product specifications include

Executive Summary Section

appearance, identity, assay, related substances, (b) (4) dissolution, content uniformity, and microbial limits. Up to 48 months real time stability data are provided to support a 48 month expiry. Additional supportive real time and accelerated stability data also support this claim. All drug product manufacturing sites have acceptable EES status as of 11-Sep-2014.

B. Description of How the Drug Product is Intended to be Used

The product is to be taken orally for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed pirfenidone treatment regimen include a titration and maintenance phase as shown below:

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the Esbriet (pirfenidone) capsule product. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable;
- Both drug substance and drug product are very stable and support the claimed four years of drug product expiry.

III. Administrative**A. Reviewer's Signature**

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date: Same date as draft review

C. CC Block

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/s/

XIAOBIN SHEN

09/16/2014

The NDA is recommended for approval from CMC perspective.

CRAIG M BERTHA

09/16/2014

I concur.

NDA 22-535

Pirfenidone Capsule

InterMune, Inc.

Xiaobin Shen, Ph.D.

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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Chemistry Review Data Sheet

1. NDA 22-535
2. REVIEW #: 3
3. REVIEW DATE: 29-Aug-2014
4. REVIEWER: Xiaobin Shen, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous DocumentsDocument Date

Original	04-Nov-2009
Amendment 0015	29-Jan-2010
Amendment 0018	12-Feb-2010
Amendment 0028	05-Mar-2010
Amendment 0031	18-Mar-2010
Amendment 0033	25-Mar-2010
Amendment 0034	25-Mar-2010
Amendment 0035	06-Apr-2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) ReviewedDocument Date

Amendment 0045	23-May-2014
Amendment 0049	04-Aug-2014

Other amendments not listed do not have CMC information for review.

7. NAME & ADDRESS OF APPLICANT:

Name: InterMune, Inc.

Chemistry Review Data Sheet

Address: 3280 Bayshore Boulevard
Brisbane, CA 94005

Representative: Marianne Armstrong, Ph.D.

Telephone: 415-840-4831

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Esbriet
- b) Non-Proprietary Name (USAN): Pirfenidone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: Not established

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 267 mg/capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

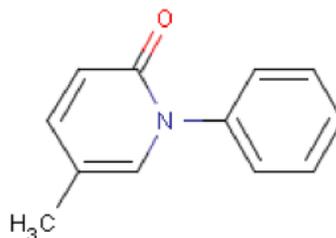
SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

5-methyl-1-phenyl-2-(1H)-pyridone;

Molecular formula: C₁₂H₁₁NO

Molecular Weight: 185.23 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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	IV			4		NA	
	III			4		NA	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	

Chemistry Review Data Sheet

(b) (4)	(b) (4)				
III		4		N/A	

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6 – DMF not available

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B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,284	Pirfenidone 400 mg capsule

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	29-Aug-2014	Dr. Xiaobin Shen
Pharm/Tox	Approval	13-Aug-2014	Dr. Timothy W. Robison
Biopharm	Not needed	NA	NA
Methods Validation	Not needed	NA	NA
EA	Adequate	30-Jul-2014	Dr. Xiaobin Shen
Microbiology	Approval	14-Aug-2014	Dr. Robert Mello

The Chemistry Review for NDA 22-535

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The NDA is recommended for approval from CMC perspective, pending satisfactory EES status.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Products

Drug substance pirfenidone is developed as a treatment for patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Its pharmacological category has not been established. Pirfenidone is a small synthetic non-peptide new molecular entity. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. Pirfenidone does not possess polymorphism.

Pirfenidone is prepared through (b) (4)

Specifications for the starting materials, reagents, and in-process control are adequate. The structure of pirfenidone was confirmed by a combination of the spectroscopic and analytic techniques. Specifications for pirfenidone drug substance include appearance, identification, assay, related substances, water content, residue on ignition, heavy metals, loss on drying and particle size distribution. The support of drug substance is referenced to DMF (b) (4) which has been deemed adequate by this reviewer on 05-Aug-2014. The drug substance retest period is (b) (4) months. The drug substance manufacturing site is pending cGMP inspection as of 29-Aug-2014.

The drug product is manufactured as size 1 capsules. Each contains 267 mg pirfenidone. There are two presentations. The white body and white cap capsules are to be marketed in the United States. The blue body and gold cap capsules are to be marketed in Europe and Canada. The two presentations (b) (4)
The excipients used include croscarmellose sodium, microcrystalline cellulose, povidone, and magnesium stearate. The capsules are supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card can

Executive Summary Section

contain 21, 42 or 63 capsules per blister card. The product specifications include appearance, identity, assay, related substances, (b) (4) dissolution, content uniformity, and microbial limits. Up to 48 months real time stability data are provided to support a 48 month expiry. Additional supportive real time and accelerated stability data also support this claim.

B. Description of How the Drug Product is Intended to be Used

The product is to be taken orally for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed pirfenidone treatment regimen include a titration and maintenance phase as shown below:

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the Esbriet (pirfenidone) capsule product. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable;
- Both drug substance and drug product are very stable and support the claimed four years of drug product expiry.

III. Administrative

A. Reviewer's Signature

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date: Same date as draft review

C. CC Block

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/s/

XIAOBIN SHEN

08/29/2014

The NDA is recommended for approval pending satisfactory EES status.

CRAIG M BERTHA

09/02/2014

I concur.

Esbriet® (pirfenidone) Capsules

NDA 22-535

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: InterMune Inc.
3280 Bayshore Boulevard
Brisbane, CA 94005

Indication: Treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. A daily dose could be as high as 9 capsules per day (2.4 gm). See dosage table below.

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

Presentation: Esbriet is a blue and gold hard gelatin capsule with markings “InterMune®” and “267 mg” printed in brown ink on the gold cap of the capsule. The drug product is supplied in child resistant HDPE bottles containing 270 capsules and in (b) (4) blister cards containing 21, 42 and 63 capsules per card.

EER Status: Recommendation Acceptable (8-Mar-2010)

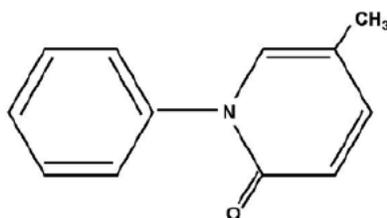
Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Microbiology Review – **Not acceptable**, J. McVey, 03-May-2010
Methods Validation – Revalidation by Agency not requested
Pharm/Tox Review- **Pending**

Original Submission: 4-Nov-2009

Post-Approval CMC Commitments: None

Drug Substance:

Pirfenidone is a synthetically derived new molecular entity. Pirfenidone is chemically described as 5-methyl-1-phenyl-2-(1H)-pyridone. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. It is very soluble in methanol, and freely soluble in ethyl alcohol, acetone and chloroform; it is sparingly soluble in 1.0 N HCl. The melting point is approximately 109°C. (b) (4) The empirical formula of pirfenidone is C₁₂H₁₁NO and the molecular weight is 185.23. The structural formula of pirfenidone is shown below:



The drug substance is manufactured by (b) (4). All information pertaining to the manufacture and quality control of the drug substance is referenced to DMF (b) (4). The drug substance was adequately characterized by UV spectroscopy, IR spectroscopy, H NMR, ¹³C NMR, mass spectroscopy and melting point. The drug substance specification includes description, identification (IR, UV), assay (HPLC), related substances (HPLC), water content (Karl Fischer), residue on ignition, heavy metals, loss on drying and particle size distribution (Laser Diffraction). (b) (4)

The drug substance contains a process impurity that is a potential mutagen. The DMF holder was asked to either reduce its level to limit the total daily exposure of NMT 1.5 µg/day or provide evidence that it is not genotoxic. The applicant submitted a response to the deficiency on 15-Apr-2010; evaluation is ongoing by Pharm/Tox.

The drug substance is stored in (b) (4). A retest period of (b) (4) months has been established for the drug substance due to the high stability of the drug substance.

Conclusion: The drug substance is **acceptable pending satisfactory evaluation of potentially mutagenic impurity.**

Drug Product:

Esbriet® (pirfenidone) capsule is available as a blue and gold hard gelatin capsule for oral administration. Each capsule contains 267 mg pirfenidone, croscarmellose sodium, microcrystalline cellulose, and povidone. The capsule is supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. Each blister card can contain 21, 42, or 63 capsules.

The drug product is manufactured by (b) (4) for InterMune Inc. Manufacturing process and excipient influence on the final product was evaluated and optimized. The finalized manufacturing processes include (b) (4). All manufacturing steps have appropriate process controls and critical process parameters were identified. Pirfenidone capsules are packaged in high density polyethylene containers with induction seals and child-resistant closures or in (b) (4) blister package configuration.

The drug product release specifications include description, identity (UV and HPLC), assay (HPLC), related substances (HPLC), (b) (4) dissolution, content uniformity, and microbial limits. Evaluation of the microbial limits was found to be unacceptable due to inadequate sample size and sensitivity of the test methods.

Up to 12 months real time stability data are provided and support a (b) (4) month expiry. The proposed regulatory methods have been validated. The drug substance and drug product have demonstrated acceptable stability.

Conclusion: The drug product is **unacceptable** due to inappropriate microbial limits assay method.

Additional Items:

- All associated Drug Master Files **except for the drug substance** DMF are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is **not recommended** for approval due to inadequate qualification of impurities in the drug substance, and inadequate microbial limits assay method.

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

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/s/

CHRISTINE M MOORE
05/03/2010
Division I Director (acting)

NDA 22-535

Pirfenidone Capsule

InterMune, Inc.

Xiaobin Shen, Ph.D.

**Division of Pulmonary, Allergy and Rheumatology Drug
Products**

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Chemistry Review Data Sheet

1. NDA 22-535
2. REVIEW #: 2
3. REVIEW DATE: 22-Apr-2010
4. REVIEWER: Xiaobin Shen, Ph.D.

04. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original	04-Nov-2009
Amendment 0015	29-Jan-2010
Amendment 0018	12-Feb-2010
Amendment 0028	05-Mar-2010
Amendment 0031	18-Mar-2010
Amendment 0033	25-Mar-2010
Amendment 0034	25-Mar-2010

04. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Amendment 0035	06-Apr-2010

7. NAME & ADDRESS OF APPLICANT:

Name: InterMune, Inc.

Chemistry Review Data Sheet

Address: 3280 Bayshore Boulevard
Brisbane, CA 94005

Representative: Marianne Armstrong, Ph.D.

Telephone: 415-466-2532

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Esbriet
- b) Non-Proprietary Name (USAN): Pirfenidone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: Not established

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 267 mg/capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

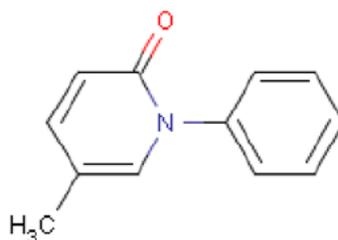
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methyl-1-phenyl-2-(1H)-pyridone;

Molecular formula: C₁₂H₁₁NO

Molecular Weight: 185.23 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	05-Apr-2010	Information request were sent to the DMF holder on 04-Mar-2010 and 12-Mar-2010. Per consultation with the Pharm/Tox reviewer Dr. Timothy W. Robison, this DMF is inadequate from a pharm/tox

Chemistry Review Data Sheet

							perspective, it is otherwise adequate from a CMC perspective.
(b) (4)	IV	(b) (4)	(b) (4)	4		NA	
	III			3	Adequate	15-Sep-2000	The supporting review is located in Vol. B5.1
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	
	III			4		N/A	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,284	Pirfenidone 400 mg capsule

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	16-Mar-2010	Xiaobin Shen
Pharm/Tox	Pending	22-Apr-2010	Dr. Timothy W. Robison
Biopharm	Not needed	NA	NA
LNC	Pending	22-Apr-2010	NA
Methods Validation	Not needed	NA	NA
DMEPA/OSE	NA	NA	NA
EA	Adequate	02-Mar-2010	Xiaobin Shen
Microbiology	Pending	22-Apr-2010	Dr. James McVey

The Chemistry Review for NDA 22-535

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable.

The drug substance DMF is inadequate at present due to the outstanding impurity qualification issue for which final data is not submitted as of 16-Apr-2010. This is a Pharm/Tox issue.

There are microbiology method validation related responses to the Agency's information request pending review.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant agrees to further tighten the total impurities specifications of both drug substance and drug product based on the release and stability experience with the first ten commercial lots. A CBE-30 will be filed to report the changes.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Products

Drug substance pirfenidone is developed as a treatment for patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Its pharmacological category has not established. Pirfenidone is a small synthetic non-peptide new molecule entity. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. Pirfenidone does not possess polymorphism.

Pirfenidone is prepared through [REDACTED] (b) (4)

[REDACTED] Specifications for the starting materials, reagents, and in-process control are adequate. The structure of pirfenidone was confirmed by a combination of the spectroscopic and analytic techniques. Specifications for pirfenidone drug substance include description, identification, assay, related substances, water content, residue on ignition, heavy metals, loss on drying and particle size distribution. The drug substance stability study was conducted at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). The results conformed to specifications. The retest period

Executive Summary Section

is (b) (4) months. The drug substance contains impurity (b) (4). This impurity is a potential mutagen existing at a level that causes more than 1.5 µg/day total daily exposure allowed by the draft genotoxic guidance. Information request was sent to the DMF holder to either reduce its level to limit a total daily exposure of not more than 1.5 µg/day or prove that it is not genotoxic. The DMF holder responded on 19-Mar-2010 that the applicant plans to conduct studies to qualify the impurity. The draft study report was submitted on 06-Apr-2010 and the final report is pending submission as of 16-Apr-2010. This issue is currently outstanding. Once the final study results are submitted, Pharm/Tox will evaluate and determine if this is a deficiency or it should be resolved through post marketing commitment or post marketing requirement.

The drug product is Esbriet capsule containing 267 mg pirfenidone, (b) (4) mg croscarmellose sodium, (b) (4) mg microcrystalline cellulose, and (b) (4) mg povidone. The opaque size 1 capsule has a blue body and gold cap and is made of hard gelatin. The capsule is supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card can contain 21, 42 or 63 capsules per blister card. The product specifications include description, identity, assay, related substances, (b) (4) dissolution, content uniformity, and microbial limits. Up to 12 months real time stability data are provided to support a (b) (4) month expiry. Additional supportive real time and accelerated stability data also support this claim.

There were (b) (4) concerns about the blister package to be used for the drug product. The applicant responded to the Agency's information request stating that the package is similar to that of currently marketed products (b) (4) further the provided test results to support the package's use. Based on all provided information, the blister package is now considered acceptable.

All IQA comments have been evaluated and resolved.

During the review, information requests were sent to the applicant. Responses to the information request are evaluated at end of this review.

B. Description of How the Drug Product is Intended to be Used

The product is to be taken orally for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed pirfenidone treatment regimen include titration and maintenance phase as shown below:

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the Esbriet (pirfenidone) capsule product. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable;
- Both drug substance and drug product are very stable and support the claimed ^{(b) (4)} of drug product expiry.

The drug substance and drug product contain impurity ^{(b) (4)}

This impurity is a structural alert with potential mutagenicity. It requires qualification or its level needs to be reduced to allow no more than 1.5 µg/day total daily exposure. At present, the applicant conducted studies to qualify, the final report is yet to be submitted and reviewed. This is a Pharm/Tox issue.

There are three responses to information requests related to the microbial limit testing method validation pending for review. These do not affect the recommendation. The drug product is a solid oral product, it does not support growth of micro organisms and all obtained microbial limit results met USP <61> and <62>.

III. Administrative**A. Reviewer's Signature**

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

6 Page(s) has 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)

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

/s/

XIAOBIN SHEN

04/22/2010

The NDA is approvable. There is a comment to be sent with the action letter.

PRASAD PERI

04/23/2010

I concur

May 13, 2010

This CMC secondary review is superseded by the Division Director Memo checked in as a REV-QUALITY-03 (General Review) on May 3, 2010 by Christine Moore, the Acting Director.

For NMEs, the ONDQA policy is for the Division Director to include a DD Memo and check it into DARRTS in place of the CMC secondary review.

Esbriet® (pirfenidone) Capsules

NDA 22-535

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: InterMune Inc.
3280 Bayshore Boulevard
Brisbane, CA 94005

Indication: Treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. A daily dose could be as high as 9 capsules per day (2.4 gm). See dosage table below.

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

Presentation: Pirfenidone capsules are supplied in child resistant HDPE bottles containing 270 capsules and in (b) (4) blister cards containing 21, 42 and 63 capsules per card.

EER Status: Recommendation Acceptable (8-Mar-20010)

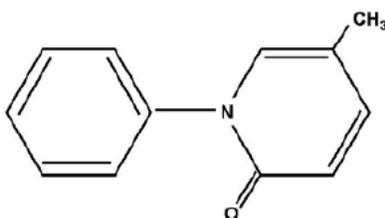
Consults: EA – Categorical exclusion granted under 21 CFR §25.31(c)
Microbiology Review - **Pending**
Methods Validation – Revalidation by Agency not requested
Pharm/Tox Review-**Pending**

Original Submission: 4-Nov-2009

Post-Approval CMC Commitments: None

Drug Substance:

Pirfenidone is a small synthetic new molecular entity. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. It is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The melting point is approximately 109°C. Pirfenidone does not possess polymorphism. Pirfenidone is chemically described as 5-methyl-1-phenyl-2-(1H)-pyridone. The empirical formula of pirfenidone is C₁₂H₁₁NO and the molecular weight is 185.23. The structural formula of pirfenidone is shown below:



The drug substance is manufactured at by (b) (4). All information pertaining to the manufacture and quality control of the drug substance is referenced to DMF (b) (4). The DMF was reviewed and found inadequate due to impurities in the drug product.

The drug substance contains a process impurity (b) (4) that is controlled at (b) (4)%. Since this impurity is a potential mutagen existing at a level > 1.5 µg/day total daily exposure at the proposed dosage levels, the DMF holder was asked to either reduce its level to limit a total daily exposure of NMT 1.5 µg/day or provide evidence that it is not genotoxic. The DMF holder responded on 19-Mar-2010 and indicated that the applicant plans to conduct studies to qualify the impurity. The draft study report will be submitted by 15-Apr-2010 and the final report about 2 weeks thereafter. This issue is currently outstanding. Once the study results are submitted, the pharm/tox team will evaluate the data and recommend an appropriate course of action.

The drug substance is controlled by testing for description, identification, assay, related substances, water content, residue on ignition, heavy metals, loss on drying and particle size distribution. (b) (4)

The drug substance is stored in (b) (4). Further, it states that photostability studies indicate that (b) (4). A retest period of (b) (4) months has been established for the drug substance due to the exceptional stability of the drug substance.

Conclusion: The drug substance is **not** satisfactory due to the qualification issue of the impurity.

Drug Product:

Esbriet® (pirfenidone) capsule is available as a blue and gold hard gelatin capsule for oral administration. The capsule is size 1 and has the markings “InterMune®” and “267 mg” printed in brown ink on the gold cap of the capsule. Each capsule contains 267 mg pirfenidone, (b) (4) mg croscarmellose sodium, (b) (4) mg microcrystalline cellulose, and (b) (4) mg povidone.

The capsule is supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card can contain 21, 42, or 63 capsules per blister card.

The drug product is manufactured by (b) (4) for InterMune Inc. Manufacturing process and excipient influence on the final product was evaluated and optimized. The finalized manufacturing processes include (b) (4)

The release specifications include description, identity, assay, related substances, (b) (4) dissolution, content uniformity, and microbial limits. Up to 12 months real time stability data are provided and support a (b) (4) **month expiry**. The proposed regulatory methods have been validated. The drug substance and drug product have demonstrated exceptional stability.

Conclusion: The drug product is acceptable.

Additional Items:

- All associated Drug Master Files **except for the drug substance** DMF are acceptable or the pertinent information has been adequately provided in the application.
- The analytical methods used in the testing procedures (release, stability, and in-process) are well known and widely used by the biopharmaceutical industry; revalidation by Agency laboratories will not be requested.

Overall Conclusion:

From a CMC perspective, the application is recommended for approval **pending satisfactory** pharm/tox qualification or the drug substance impurity, microbiology evaluation pertaining to microbial limit test methods validation, and adequate responses to labeling comments.

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

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

/s/

PRASAD PERI
04/09/2010

NDA 22-535

Pirfenidone Capsule

InterMune, Inc.

Xiaobin Shen, Ph.D.
Division of Pulmonary, Allergy and Rheumatology Drug
Products

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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA 22-535
2. REVIEW #: 1
3. REVIEW DATE: 05-Apr-2010
4. REVIEWER: Xiaobin Shen, Ph.D.

04. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

NA

04. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Amendment 0015

Amendment 0018

Amendment 0028

Amendment 0031

Amendment 0033

Amendment 0034

Other amendments older than the last listed do not have CMC related information for review.

Document Date

04-Nov-2009

29-Jan-2010

12-Feb-2010

05-Mar-2010

18-Mar-2010

25-Mar-2010

25-Mar-2010

7. NAME & ADDRESS OF APPLICANT:

Chemistry Review Data Sheet

Name: InterMune, Inc.
Address: 3280 Bayshore Boulevard
Brisbane, CA 94005
Representative: Marianne Armstrong, Ph.D.
Telephone: 415-466-2532

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Esbriet
- b) Non-Proprietary Name (USAN): Pirfenidone
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: NDA 505(b)(1)

10. PHARMACOL. CATEGORY: Not established

11. DOSAGE FORM: Capsule

12. STRENGTH/POTENCY: 267 mg/capsule

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: Rx OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

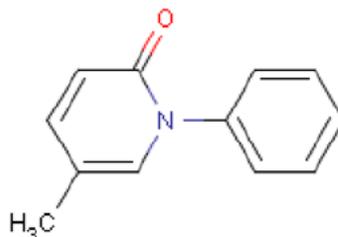
SPOTS product – Form Completed

Not a SPOTS product

Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

5-methyl-1-phenyl-2-(1H)-pyridone;

Molecular formula: C₁₂H₁₁NO

Molecular Weight: 185.23 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	(b) (4)	1	Inadequate	05-Apr-2010	Information request were sent to the DMF holder on 04-Mar-2010 and 12-Mar-2010. Per consultation with the Pharm/Tox reviewer Dr. Timothy W. Robison, this DMF is inadequate from a

Chemistry Review Data Sheet

							pharm/tox perspective, it is otherwise adequate from a CMC perspective.
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate	NA	NA
	III			3	Adequate	15-Sep-2000	The supporting review is located in Vol. B5.1
	III			4	Adequate	N/A	NA
	III			4	Adequate	N/A	NA
	III			4	Adequate	N/A	NA
	III			4	Adequate	N/A	NA
	III			4	Adequate	N/A	NA
	III			4	Adequate	N/A	NA

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	67,284	Pirfenidone 400 mg capsule

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not needed	NA	NA
EES	Acceptable	16-Mar-2010	Xiaobin Shen
Pharm/Tox	Pending	01-Apr-2010	Dr. Timothy W. Robison
Biopharm	Not needed	NA	NA
LNC	Pending	01-Apr-2010	NA
Methods Validation	Not needed	NA	NA
DMEPA/OSE	NA	NA	NA
EA	Adequate	02-Mar-2010	Xiaobin Shen
Microbiology	Pending	25-Mar-2010	Dr. James McVey

The Chemistry Review for NDA 22-535

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is approvable.

The drug substance DMF is inadequate at present due to the outstanding impurity qualification issue for which qualification data is expected by 15-Apr-2010. This is a Pharm/Tox issue.

The blister packaging container closure of the product has (b) (4) risk, detailed comments were communicated to the applicant for resolution.

Additionally, there are three information requests regarding the validation of microbial limit test method. The responses are still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

The applicant agrees to further tighten the total impurities specifications of both drug substance and drug product based on the release and stability experience with the first ten commercial lots.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance(s) and Drug Products

Drug substance pirfenidone is developed as a treatment for patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Its pharmacological category has not established. Pirfenidone is a small synthetic non-peptide new molecule entity. It is a white to pale yellow powder that is slightly soluble in water (19 mg/mL) at 25°C and non-hygroscopic. Pirfenidone does not possess polymorphism.

Pirfenidone is prepared through (b) (4)

Specifications for the starting materials, reagents, and in-process control are adequate. The structure of pirfenidone was confirmed by a combination of the spectroscopic and analytic techniques. Specifications for pirfenidone drug substance include description, identification, assay, related substances, water content, residue on

Executive Summary Section

ignition, heavy metals, loss on drying and particle size distribution. The drug substance stability study was conducted at both long term (25°C/60% RH) and accelerated conditions (40°C/75% RH). The results conformed to specifications. The retest period is (b) (4) months. The drug substance contains impurity (b) (4). This impurity is a potential mutagen existing at a level that causes more than 1.5 µg/day total daily exposure allowed by the draft genotoxic guidance. Information request was sent to the DMF holder to either reduce its level to limit a total daily exposure of not more than 1.5 µg/day or prove that it is not genotoxic. The DMF holder responded on 19-Mar-2010 that the applicant plans to conduct studies to qualify the impurity. The draft study report will be submitted by 15-Apr-2010 and the final report about 2 weeks thereafter. This issue is currently outstanding. Once the study results are submitted, Pharm/Tox will evaluate and determine if this is a deficiency or it should be resolved through post marketing commitment or post marketing requirement.

The drug product is Esbriet capsule containing 267 mg pirfenidone, (b) (4) mg croscarmellose sodium, (b) (4) mg microcrystalline cellulose, and (b) (4) mg povidone. The opaque size 1 capsule has a blue body and gold cap and is made of hard gelatin. The capsule is supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. The blister card can contain 21, 42 or 63 capsules per blister card. The product specifications include description, identity, assay, related substances, (b) (4) dissolution, content uniformity, and microbial limits. Up to 12 months real time stability data are provided to support a (b) (4) month expiry. Additional supportive real time and accelerated stability data also support this claim.

The blister cards are stated to be (b) (4) but do not provide adequate (b) (4). There are also other product name, dosage form and strength related issues that make for the packaging blister card packaging system unacceptable. All comments have been communicated to the applicant in an information request fax.

All IQA comments have been evaluated and resolved.

During the review, information requests were sent to the applicant. Responses to the information request are evaluated at end of this review.

B. Description of How the Drug Product is Intended to be Used

The product is to be taken orally for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed pirfenidone treatment regimen include titration and maintenance phase as shown below:

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsule three times a day with food
15 +	2403	(3) 267 mg capsule three times a day with food

Executive Summary Section

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided information on the chemistry, manufacturing, and controls of the Esbriet (pirfenidone) capsule product. The product is recommended for approval based on the following:

- The drug substance and product specifications provided adequate controls;
- The drug product excipients are of USP/NF grade;
- The drug product container closure systems are acceptable though with some concerns (noted below);
- Both drug substance and drug product are very stable and support the claimed (b) (4) years of drug product expiry.

The drug substance and drug product contain impurity (b) (4). This impurity is a structural alert with potential mutagenicity. It requires qualification or its level needs to be reduced to allow no more than 1.5 µg/day total daily exposure. At present, the applicant plans to qualify the impurity and provide draft data by 15-Apr-2010. This is a Pharm/Tox issue.

The blister card package configuration does not provide adequate (b) (4). The dosage form and strength information on the packaging cartons need to be revised.

There are also three outstanding information requests related to the microbial limit testing method validation.

The packaging and microbial related information request can be resolved with reasonable effort.

III. Administrative**A. Reviewer's Signature**

Review is digitally signed in DARRTS.

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

38 Page(s) has 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)

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

/s/

XIAOBIN SHEN

04/05/2010

The NDA is approvable pending resolution of several issues communicated to the applicant already.

PRASAD PERI

04/05/2010

I concur

OND Division of Pulmonary and Allergy Products

NDA: 22-535

Applicant: InterMune Inc.

Stamp Date: 4-Nov-2009

PDUFA Date: 4-May-2010 (6 months)

ONDQA 3 month date: 4-Feb-2010

Proposed Proprietary Name: Trade Name Capsules

Established Name: (pirfenidone)

Dosage form and strength: capsules, 267 mg

Route of Administration: oral

Indications: The treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Maximum daily dose is 3 capsules three times a day (2403 mg/day)

PAL: Prasad Peri, Ph.D. Branch II/DPA I/ONDQA

Filability recommendation: Acceptable for filing

Review team recommendation: Single primary reviewer (Xiaobin Shen, PhD)

Time goals:

- **Initial Quality Assessment in DFS: by 15-Jan-2010**
- **Chemistry filing memo in DFS: by 15-Jan-2010**
- Filing decision "Day 45": 9-Dec-2009
- Filing review issues "Day 74": 15-Jan-2010
- **Chemistry Review (DR/IR) letter: by 4-Feb-2010**
- Mid-cycle meeting "Month 3": 4-Mar-20010
- Wrap Up: ~4-Apr-2010
- **Final Chemistry Review "Month 5" in DFS: by 5-Apr-2010**
- PDUFA: 4-May-2010

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Biopharm/ClinPharm	To be determined by Primary Reviewer
CDRH	<i>Not Applicable</i>
EA	To be assessed by Primary Reviewer
EES	EER sent to Office of Compliance on 16-Nov-2009
DMETS	<i>Labeling consult request will be sent as part of DPAP's request.</i>
Methods Validation	<i>Validation may be requested of FDA labs after test methods are finalized.</i>
Microbiology	<i>May be necessary as (b) (4) ranges from up to (b) (4) %.</i> <i>Issue of (b) (4) to be assessed.</i>
Pharm/Tox	<i>DS and DP Impurities to be qualified</i>

Summary:

- This is a eCTD format NDA with electronic labeling provided in SPL format. IND referenced for this application is IND 67284. There is a Quality Overall Summary. This NDA is filed as a 505(b)(1) application. Note this drug has been granted an orphan status and the PDUFA goal is a 6 month clock.

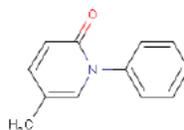
- InterMune licensed pirfenidone from Marnac, Inc. (Marnac), the product innovator, in March 2002 for development as a treatment for idiopathic pulmonary fibrosis (IPF). Marnac had previously conducted early Phase 1 trials with a 400-mg capsule dosage strength of pirfenidone (note that this formulation included (b) (4))
- InterMune subsequently conducted an early Phase 1 trial with the 400-mg capsule dosage form as well as providing it for several investigator-sponsored studies.
- Shionogi & Co., Ltd. (Shionogi) licensed pirfenidone from Marnac for marketing in Japan and developed a 200-mg tablet dosage form. Shionogi used the 200-mg tablet dosage form in all clinical studies they sponsored. Clinical data from both Marnac and Shionogi studies that use the 400-mg capsule or 200-mg tablet dosage forms are included in this application. After the completion of preformulation studies and an assessment of the clinical drug dosage in IPF, InterMune decided to develop a hard gelatin capsule dosage form.

Drug Substance

- Drug substance pirfenidone chemical name 2(1H)-Pyridinone, 5-methyl-1-phenyl,
- CAS Registry Number: 53179-13-8
- Information concerning the procedures and controls for assuring the proper identification, quality, purity, and strength of pirfenidone are incorporated by reference to (b) (4) Type II Drug Master File (DMF) (b) (4) dated 17 October 2008. A Letter of Authorization from (b) (4) is provided in Section 1.4.1.

Molecular Formula: C₁₂H₁₁NO

Molecular Weight: 185.23 g/mol



Parameter	Results
Physical description	White to pale yellow powder
Solubility	Very soluble in methanol. Freely soluble in ethyl alcohol, acetone, and chloroform. Sparingly soluble in 1.0 N hydrochloric acid. Slightly soluble in water. Insoluble in 1.0 N sodium hydroxide
Melting range	Between 106°C and 112°C
Particle size distribution	The (b) (4) is not more than (b) (4) μm
Potential isomerism	Pirfenidone does not possess any stereocenters and therefore is not subject to stereoisomerism.

Table 2.3.S-2 InterMune Drug Substance Information

Parameter	Results
Solubility at 25°C	
Acetone, acetonitrile, chloroform, dimethoxyethane, dimethylformamide, dimethylsulfoxide, ethanol, ethyl acetate, isopropyl alcohol, methanol, toluene	77 to 100 mg/mL (at 48 h)
Triethylamine 5	mg/mL
Water 19	mg/mL
pH Solubility, pH range of 1 to 10	19 to 22 mg/mL (at 48 h)
Partition Coefficient (Log P)	0.9
Melting Point	Between 106°C and 112°C
Hygroscopicity	Pirfenidone is not hygroscopic
Intrinsic Dissolution	
Pure water	(b) (4)
Simulated gastric fluid	
Simulated intestinal fluid	
Particle Size Distribution	
Polymorphism	

NMT = not more than; h = hour; min = minute

- The drug substance structure and physical properties are shown in the tables above which is reproduced from the application. The synthetic scheme is shown below. The drug substance characterization is performed by various spectroscopic and spectrometric techniques. The impurities and their highest observed levels are provided in the table reproduced from the application on the following page. Note that potential impurity (b) (4) is a potential structural alert and the levels of this impurity in the final drug substance should be controlled.
- The drug substance is packaged in (b) (4). The container is purported to comply with 21 CFR 177 regulations for contact with APIs. Additional information is referenced in DMF (b) (4).



Figure 2.3.S-1 Manufacturing Process Flow Diagram

Table 2.3.S-4 Structures of Potential Impurities of Pirfenidone

Chemical Name (CAS No.)	Code Name	Structural Formula	Potential Impurity Source	Highest Observed Level (b) (4)
[Redacted Content]				

Comment to sponsor:

Provide the observed levels of impurity (b) (4) in the final drug substance.

Drug Product

- InterMune has developed both 133-mg and 267-mg capsule dosage strengths. The 267-mg capsule dosage strength was used in a safety and pharmacokinetic Phase 1 study and in InterMune’s Phase 3 clinical trials, PIPF-004 and PIPF-006 while the 133 mg dose capsules were used only in the PIPF-004 trial.
- The proposed commercial drug product is an immediate release 267-mg hard gelatin capsule dosage form. The formulation and general manufacturing process for the 267-mg capsule has been consistent throughout the clinical development program. Since the clinical data from 400-mg capsules as well as 200-mg tablets have been provided as supportive data in this application, certain comparisons such as the in vitro dissolution of these dosage forms have been made and data are provided in appropriate sections.
- The drug product formulation is provided in the table reproduced from the NDA below. The appearance of the drug product is a capsule, size #1, with a gold opaque cap and blue opaque body. The capsule is imprinted with “InterMune® 267 mg” in brown ink. Capsule contains “white to pale-yellow” powder describes the solid oral dosage form. For stability purposes the “InterMune® 267 mg” identifier mark is represented by two brown bands that have a total ink surface area greater than or equal to the identifier mark.

Table 2.3.P.1-2 Ink (Brown S-1-16530) Components, Quality Standards, and Composition

Component	Quality Standard	CFR Reference	Colour Index Number
Shellac Glaze (b) (4)	USP/NF ^a	21 CFR 73.1, 73.1001; 27 CFR 21.80	NA
(b) (4)	NF	21 CFR 73.1	NA
(b) (4)	USP	21 CFR 73.1, 73.1001	NA
Iron oxide black	NA	21 CFR 73.1200	(b) (4)
Iron oxide red	NF	21 CFR 73.1200	(b) (4)
Propylene glycol	USP/FCC	21 CFR 184.1666	NA
Iron oxide yellow	NF	21 CFR 73.1200	(b) (4)
Ammonium hydroxide (b) (4)	NF/FCC	NA	NA

NA = Not applicable; FCC = Food Chemical Codex; NF = National Formulary;
 USP = United States Pharmacopeia
^a Shellac (b) (4) are USP/NF grade.

Table 2.3.P.1-1 Drug Product Components, Quality Standards, and Composition

Component	Quality Standard	Function	mg/Capsule
Pirfenidone	In-house ^a	(b) (4)	267
Croscarmellose, sodium ^f	NF		(b) (4)
Microcrystalline cellulose ^{b, f}	NF		
Povidone ^f	USP		
Magnesium stearate ^f	NF		
(b) (4)	USP		
Blue body and gold cap, opaque, size 1, hard gelatin capsule shells with identifier mark ^d	(b) (4) DMF (b) (4)	Capsule	
Printing ink, Brown (b) (4)	DMF	Identification mark	
Total weight per capsule			325.0

NF = National Formulary; USP = United States Pharmacopeia; qs = quantity sufficient

^a Refer to Section 2.3.S.4 [Pirfenidone, (b) (4)] for drug substance acceptance criteria.

(b) (4)

^f Excipients used are of pharmaceutical grade.

- The contents of the printing ink are reported in the table on the previous page.
- Note that the drug product is supplied in either HDPE bottles of 270 capsules, or blisters of 14 day titration pack (63 capsules in blisters) or blisters of a 4 week maintenance package (carton containing 253 capsules in blisters)
- The tablet formulation used in the Shionogi trial and commercially approved in Japan is shown below.

Table 2.3.P.2-3 Tablet Formulation

Component ^a	Amount (mg/tablet)
(b) (4)	

^a Shionogi formulation and dosage form used in the supportive Phase 3 Study (SP3).

CRITICAL ISSUES

- Has all information requested during the IND phases, and at the pre-NDA meetings been included? No.
- Residual Solvents: Although comments were made in the preNDA meeting about the sponsor to certify that the drug product meets, USP <467> requirements, it is not clear if this has been made. A comment is being sent.

- **Dissolution**

The applicant plans to use USP Apparatus II (paddle) using deionized water (1000 mL). It is claimed that the proposed conditions offer (b) (4) the sink conditions for the drug product. Yet, the acceptability of the dissolution method should be evaluated by the biopharm team. See below.

- **Overage in the formulation.**

None proposed.

- **Excipients from Animal Origin.**

Capsules are obtained from (b) (4) and the applicant claims that they meet the EU regulations for BSE/TSE. The reviewer needs to confirm that they meet the US FDA BSE/TSE requirements as well in the DMF.

- **OVI in the drug Product**

The applicant has not provided any statements or references to include that the drug product or excipients meet the new USP <467> requirements. The reviewer will need to follow up with this requirement. This proposed limit is based on ICH acceptable limits and will need to be justified.

It is not clear what the stability of the (b) (4) will be with levels as high as (b) (4) ppm of (b) (4)

Comment for the 74 day letter: Provide certification from the excipient manufacturers that their products conform to USP <467> limits. Alternately certify that the drug product meets the USP <467> requirements.

- **Manufacturing differences between pilot and commercial scales.**

Pilot scale and stability batches used (b) (4) size and the commercial scale batches are proposed to be (b) (4) size. (b) (4) batches were manufactured and their process parameters compared in the table below. The reviewer needs to evaluate the differences seen in various parameters within the pilot scale batches and between the pilot scale and (b) (4) batches.

Table 2.3.P.2-11 Process Parameters Used for Representative Drug Product Batches, continued

Batch Number:	04JM-262	0701451	0703447	0803833	0910164 ^c
Batch Usage:	Clinical Study PIPF-005	Clinical Study PIPF-006 ^a	Primary Stability	(b) (4)	(b) (4)
(b) (4)					

GMP status of the drug substance/drug product manufacturing sites.

DS site has already been found to be acceptable. During the preNDA meeting there was a question of qualifying an alternate DS manufacturing site; however no reference to this site has been provided in the application. This may likely be a post approval issue.

- **Safety of imprinting inks.**

All ingredients in the printing inks for the capsule are referenced to appropriate food additive regulations. See table above.

- **Dissolution of the drug product.**

The proposed dissolution method and criteria will be assessed and finalized based on the adequacy of the test methods and the available batch release and stability data. Note that the dissolution medium contains 1000 mL of deionized water. The solubility of the drug substance is quite high 19-22 mg/mL in a wide range of pH 1-10, indicating that the drug product dissolution is independent of pH. The applicant claims that their drug substance falls under a BCS 1 classification. The applicant submitted results from a study of varying particle size distribution ((b) (4) microns) to the drug product dissolution. The sponsor proposes using a sinker which is acceptable by USP. For all lots of drug substance with varying particle size distribution, the dissolution results were about (b) (4) % in 30 minutes. Hence the applicant proposes only a (b) (4) for particle size distribution (b) (4) microns. Note that the reviewer should discuss if dissolution or disintegration is a better method for this product.

Table 2.3.P.2-6 Dissolution Profile Parameters

Dissolution Apparatus ^a	USP Apparatus II (Paddle)
Media	Deionized water
Media Volume	1000 mL
Media Temperature	37.0°C ± 0.5°C
Paddle Speed	50 RPM
Detection Method ^b	
UV Cell	2.0 mm path length
Wavelength	318 nm

UV = ultraviolet

^a Dissolution is conducted using a sinker.

^b ATM-IFL-J0001.

Table 2.3.P.2-7 Comparative Dissolution Profile Data

Dosage Strength and Form: [Batch Number]:	267-mg Capsule [Lot 04JM-262]	133-mg Capsule [Lot 0603965]	267-mg Capsule [Lot 0701451]	400-mg Capsule [Lot M0190]	267-mg Capsule [Lot 0801545]	200-mg Tablet [Lot NA]
Manufacturing Site:	(b) (4)					
Lot Usage:	Clinical Study PIPF-005	Clinical Study PIPF-004 ^a	Clinical Study PIPF-006 ^a	Clinical Study PIPF-002	Clinical Study PIPF-012	Clinical Studies SP2 and SP3
	Mean Pirfenidone Dissolved, % (%RSD)					
Number of Units ^b	(b) (4)					
Time (minutes)	(b) (4)					
5	(b) (4)					
10	(b) (4)					
15	(b) (4)					
20	(b) (4)					
30	(b) (4)					
45	(b) (4)					
60	(b) (4)					

NA = not available; NS = not sampled; VA-CSP = Veterans Affairs Cooperative Studies Program

^a The same pirfenidone capsule manufacturing process was used for all clinical trial material used in PIPF-004 and PIPF-006

(b) (4)

• Degradation products.

The sponsor indicates that there are no degradants/impurities observed in the drug product at release or stability (LOQ (b) (4) PPM for pirfenidone). Yet, the proposed limit for Total Impurities is NMT (b) (4)%. There is good rationale for the reviewer to ask the applicant to tighten the limits for Total Impurities to reflect the data observed.

Comment: Revise the limits for Total Impurities to reflect the data observed.

• Sensitivity of product to moisture and light.

The drug product is not hygroscopic and a photostability study on capsules demonstrates that the (b) (4). The data seem to suggest that the drug product is very stable.

• Microbial limits in the drug product.

Note that the drug product holds about (b) (4) although the proposed limits is (b) (4)%. As per (b) (4) of the dosage form is more critical and hence the applicant will be asked to provide this. The proposed limits for are Total viable aerobic count ≤ (b) (4) CFU/g, Total yeast and mold counts ≤ (b) (4) CFU/g, *E. coli*: Absent, *Salmonella sp.*: Absent. *S. aureus*: Absent and *P. aeruginosa*: Absent. These tests are done as per USP <61> and USP <62>. The acceptability of the proposed specs should be discussed with the microbiologist.

Comment: Provide the water activity of the proposed capsules.

• Analytical methods

The (b) (4) was changed in 2008 to be more specific and to provide more details on the inspection procedure. The (b) (4) was revised on 16 January 2009 to (b) (4). The lower limit of quantitation (LLOQ) for the impurity/degradation was (b) (4). The (b) (4) was gained by (b) (4).

(b) (4) μL for assay to (b) (4) μL for impurity analysis. Validation of the Assay/Impurities, Dissolution, and Microbial testing are provided and the reviewer will need to assess them. Note that since the drug product is (b) (4) % by weight, the sponsor will use the weight instead of (b) (4) for the Uniformity of Dosage Content which is acceptable by USP.

- **Expiration dating period of the drug product.**

Note that the applicant is proposing a (b) (4) months shelf life. Based on the preliminary evaluation of the data, (b) (4) months may be approved. The proposed labeling indicates that the drug product is to be stored at (b) (4) 25°C (b) (4) -77°F); excursions to 15-30°C [59-86°F].

- **Bulk Drug Product Stability Packaging Data and Protocol**
None proposed

- **Preliminary comments on labeling.**
None.

Table 2.3.P.2-5 Representative Batch Usage for Dissolution Profile Evaluation

Batch Number	Dosage Strength and Form	Manufacturing Site	Clinical Study Usage
0603965	133-mg capsule	(b) (4)	PIPF-004 (Phase 3 Study)
04JM-262	267-mg capsule		PIPF-005 (Renal Effect Study)
0701451	267-mg capsule		PIPF-006 (Phase 3 Study)
0801545	267-mg capsule		PIPF-012 (Open-label Study)
M0190	400-mg capsule		PIPF-002 (Open-label Study)
NA	200-mg tablet		SP2, SP3

(b) (4)

Table 2.3.S-5 Pirfenidone Acceptance Criteria

Test	Analytical Methods ^a	Acceptance Criteria
Appearance	Visual	White to pale yellow powder
Identification		
IR	USP <197K>	IR spectrum corresponds to standard
UV	USP <197U>	UV spectrum corresponds to standard
Assay (calculated on a dried basis)	HPLC	(b) (4) %
Chromatographic purity		
Purity HPLC		NLT (b) (4) %
(b) (4)		NMT (b) (4) %
(b) (4)	HPLC	NMT (b) (4) %
(b) (4)	HPLC	NMT (b) (4) %
(b) (4)	HPLC	NMT (b) (4) %
Largest unknown impurity	HPLC NM	T (b) (4) %
Total impurities	HPLC	NMT (b) (4) %
Water content (Karl Fisher)	USP <921> Method 1a	NMT (b) (4) %
Residue on ignition (Gravimetric)	USP <281>	NMT (b) (4) %
Heavy metals	USP <231> Method II	NMT (b) (4) ppm
Loss on drying	USP <731>	NMT (b) (4) %
Particle Size (b) (4)	Laser diffraction	NMT (b) (4) μm

NLT = no less than; NMT = not more than; USP = United States Pharmacopeia; IR – infrared; UV = ultraviolet; HPLC = high performance liquid chromatography

^a Analytical methods and validation reports are provided in (b) (4) DMF (b) (4) dated 17 October 2008, Section 3.2.S.4.2 and Section 3.2.S.4.3, respectively.

^b Also referred to as (b) (4)

Table 2.3.P.5-1 Drug Product Acceptance Criteria

Test	Analytical Method ^c	Acceptance Criteria
Appearance	ATM-IFL-J0012	A capsule, size #1, with a gold opaque cap and blue opaque body. The capsule is imprinted with "InterMune [®] 267 mg" in brown ink ^a . Capsule contains white to pale-yellow powder
Identity		
UV	USP <197>	Exhibit maxima and minima at the same wavelengths as Pirfenidone Reference Standard
HPLC retention time	ATM-IFL-J0002	Peak retention time consistent with Reference Standard
Assay by HPLC	ATM-IFL-J0002	(b) (4) % (b) (4)
Impurities by HPLC ^b		
No individual impurity	ATM-IFL-J0002	(b) (4)
Total impurities	(b) (4)	(b) (4)
Dissolution	ATM-IFL-J0001	$Q \geq$ (b) (4) % of label claim in 30 minutes
Dosage Form Uniformity (Weight Variation)	USP <905>	Meet USP <905> requirements
Microbial Limits		
Total aerobic microbial count (Total plate)	USP <61> (070002)	NMT (b) (4) CFU/g
Total combined mold and yeast count		NMT (b) (4) CFU/g
Staphylococcus aureus	USP <62> (070005)	Negative
Pseudomonas aeruginosa		Negative
Escherichia coli		Negative
Salmonella species		Negative

HPLC = high-performance liquid chromatography; NMT = not more than; USP = United States Pharmacopeia; UV = ultraviolet



Supporting NDA or IND: None.

Supporting DMF: (b) (4)

DMF	TYP	HOLDER	ITEM REFERENCED	COMMENTS
(b) (4)	E		(b) (4)	Review needed
	II			

* NOTE THAT DMFS ON CONTAINER CLOSURE SYSTEMS WILL NEED TO BE PROVIDED.

The following facility will be responsible for the manufacture of the drug substance and will be ready for inspection at the time of NDA submission. (b) (4) performs the manufacturer's release of the Drug Substance and conducts stability testing. InterMune reviews the Certificate of Compliance, Certificate of Analysis and other associated documentation supplied by (b) (4) and performs the final sponsor release of the drug substance used in drug product manufacture.

Manufacturing Facility

(b) (4)

United States Agent

(b) (4)

United States Contact Information

(b) (4)

The following facilities will be responsible for the manufacture, stability testing, release, packaging, labeling and distribution of the drug product and will be ready for inspection at the time of NDA submission. The commercial lots will be labeled and distributed at the (b) (4) InterMune is responsible for the release of the drug product.

Stability Testing

(b) (4)

Contact Information

(b) (4)

Bulk Drug Product Manufacturing and Release Testing

(b) (4)

Contact Information

(b) (4)

Finished Drug Product Manufacturing

(b) (4)

(b) (4)

(b) (4)

Contact Information

(b) (4)

CHEMISTRY NDA FILEABILITY CHECKLIST

IS THE CMC SECTION OF APPLICATION FILEABLE? Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?		X	12 months stability data provided.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been	X		

	included?			
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		In drug product QOS.
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	

Preliminary CMC comments for the 74 day letter

1. Provide a letter of authorization to review DMF (b) (4) in support of your application.
2. Provide letters of authorization for all components of the container closure system used to package your drug product.
3. Provide certification from the excipient manufacturers that their products conform to USP <467> limits. Alternately certify that the drug product meets the USP <467> requirements.
4. Provide the (b) (4) of the proposed capsule dosage form.
5. Provide the observed levels of impurity (b) (4) in the final drug substance.
6. Revise the limits for Total Impurities in the drug substance and drug product to reflect the data observed.

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/

PRASAD PERI
01/13/2010
Comments for sponsor

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 22535/000
Org. Code: 570
P: 1
Stat. Date: 04-NOV-2009
PDUFA Date: 23-NOV-2014
Action Goal:
District Goal: 24-SEP-2014

Sponsor: INTERMUNE INC
3280 BAYSHORE BLVD
BRISBANE, CA 94005
Brand Name: ESBRIET (PIRFENIDONE CAPSULES)
Estab. Name:
Generic Name: PIRFENIDONE CAPSULES
Product Number; Dosage Form; Ingredient; Strengths
001; CAPSULE; PIRFENIDONE; 267MG

FDA Contacts: X. SHEN Prod Qual Reviewer 3017961411
Y. LIU Product Quality PM 3017961926
J. LEE Regulatory Project Mgr 3017963769
C. BERTHA Team Leader 3017961646

Overall Recommendation: ACCEPTABLE on 11-SEP-2014 by R. MOORE () 2404029988
PENDING on 23-JUN-2014 by EES_PROD
ACCEPTABLE on 08-MAR-2010 by A. ALEXANDROW (HFD-001) 3017965363

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
(b) (4)

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 21-JUL-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No:
AADA:
Responsibilities: FINISHED DOSAGE STABILITY TESTER
Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-JUL-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 24-JUN-2014

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: (b) (4) AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-SEP-2014

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

NDA 22535/000
570
1

Sponsor: INTERMUNE INC
3280 BAYSHORE BLVD
BRISBANE, CA 94005

Brand Name: Esbriet (pirfenidone capsules)

Estab. Name:

Generic Name: PIRFENIDONE CAPSULES

Product Number; Dosage Form; Ingredient; Strengths
001; CAPSULE; PIRFENIDONE; 267MG

Sponsor: INTERMUNE INC
3280 BAYSHORE BLVD
BRISBANE, CA 94005

Brand Name: Esbriet (pirfenidone capsules)

Estab. Name:

Generic Name: PIRFENIDONE CAPSULES

Product Number; Dosage Form; Ingredient; Strengths
001; CAPSULE; PIRFENIDONE; 267MG

Goal: 05-MAR-2010

Application: NDA 22535/000

Code: 570

Priority: 1

Approval Date: 04-NOV-2009

Final Decision Date: 04-MAY-2010

Approval Goal:

Approval Goal: 05-MAR-2010

FDA Contacts: D. HENRY Project Manager 301-796-4227
X. SHEN Review Chemist 301-796-1411
P. PERI Team Leader (HFD-820) 301-796-1730

Overall Recommendation: ACCEPTABLE on 08-MAR-2010 by A. INYARD ()

Attachment: CFN: (b) (4) FEI: (b) (4)

(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER

Profile: CAPSULES, PROMPT RELEASE OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-FEB-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER

Profile: CAPSULES, PROMPT RELEASE **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-NOV-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORIES "ALSO"
(DRUGS) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 08-MAR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-DEC-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE
