

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022405Orig1s000

CHEMISTRY REVIEW(S)

ONDQA Division Director's Memo
NDA 22-405, Vandetanib Tablets, 100 and 300 mg
Date: 22-MAR-2011

Introduction

Vandetanib tablets are immediate-release (IR), film-coated tablets available in 100 mg and 300 mg strengths [REDACTED] (b) (4). The inactive ingredients in the vandetanib tablet core are conventional and include; dicalcium phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet film-coat is also conventional and consists of hypromellose 2910, polyethylene glycol 300, and titanium dioxide.

The recommended dose of vandetanib is 300 mg once daily, with or without food. Patients who experience significant side effects may have their dose reduced to 200 mg (two, 100 mg tablets) or 100 mg vandetanib daily.

No trade name is currently proposed for this product, and the finalized Chemistry, Manufacturing and Controls review (22-DEC-2010) does not recommend approval of a specified trade name. The Applicant proposed a new trade name in updated labeling on 18-MAR-2011; however, this submission was not reviewed by any discipline due to the late timing.

ONDQA recommends approval of this NDA. This recommendation does not cover the establishment of a trade name.

Administrative

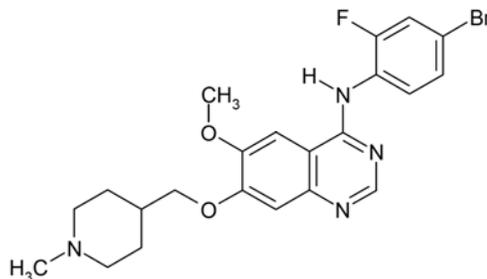
The original submission of this 505(b)(1) NDA was received 07-JUL-2010 from iPR Pharmaceuticals, Inc. (Canovanas, Puerto Rico). Eight (8) solicited CMC amendments were also reviewed during the review cycle. All Chemistry, Manufacturing and Controls assessment is captured in the following reviews, respectively: Chemistry Review #1 for both drug substance and drug product (both dated 07-DEC-2010), Biopharmaceutics Review #1 (dated 08-DEC-2010), and final CMC memorandum (dated 23-DEC-2010).

The NDA is supported by IND 60,042 and eight (8) drug master files (DMFs). Consults for EES (15-DEC-2010), Pharmacology/Toxicology (10-DEC-2010), Clinical Pharmacology (09-DEC-2010), Biopharm (08-DEC-2010), and DMEPA (for Trade Name, 22-DEC-2010) were all acceptable. Several outstanding items from the 07-DEC-2010 CMC review of drug product are captured and deemed to be acceptable in the final CMC memo (23-DEC-2010). Additional container labeling recommendations from DMEPA (see 22-DEC-2010 review) were identified and are also discussed in the CMC drug product review dated 07-DEC-2010. Note that trade name discussions occurred separately between DMEPA and the Applicant throughout the review cycle, and as of the date of this review, an acceptable trade name has not been proposed or confirmed.

This NDA is recommended for approval from a Chemistry, Manufacturing and Controls standpoint.

Drug Substance (Vandetinib)

Chemical Name: N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]quinazolin-4-amine



Molecular formula

C₂₂H₂₄BrFN₄O₂

Relative molecular mass

475.36

Vandetinib is a new molecular entity. It has two pK_a values:

(b) (4)

It is practically insoluble in water or basic pH but soluble in acidic pH. Vandetinib is considered as a BCS Class II compound. The proposed **re-test period of** when stored at the recommended container closure system (protected from light) at ambient storage conditions is granted.

(b)

(4)

Drug Product (Vandetinib Tablets, 100 and 300 mg)

The drug product is manufactured

(b) (4)

Excipients used in the formulation are conventional and include dicalcium phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet film-coat consists of hypromellose 2910, polyethylene glycol 300, and titanium dioxide.

The Applicant employed a risk-based, QbD approach to the development of vandetanib tablets. AstraZeneca (AZ) defined a quality target product profile (QTPP) along with critical quality attributes (CQAs) for the drug product. Risk assessment processes used throughout development defined the investigations performed to gain a thorough understanding of vandetanib tablets. The investigations covered a wide range of input and material attributes as well as process parameters and led to a clear understanding of the relationships between, and impact of, the parameters investigated on the CQAs. AZ used this understanding to define a vandetanib tablet design space and control strategy that ensures delivery drug product that consistently meets the required quality.

The commercial packaging is 30-count HDPE bottles. ONDQA recommends granting a 36 month expiry for both strengths of this drug product when stored in the commercial packaging at controlled room temperature; 25°C (77°F); excursions permitted to 15-30°C (59-86°F). **This is to be communicated in the action letter.**

Respectfully submitted,

Richard (Rik) Lostritto, Ph.D., Director
ONDQA, Division-I

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/s/

RICHARD T LOSTRITTO
03/22/2011

MEMORANDUM

TO: NDA 22-405

FROM: Wendy I. Wilson-Lee, Ph.D., Review Chemist
Debasis Ghosh, Ph.D, Review Chemist

SUBJECT: FINAL CMC ACTION RECOMMENDATION - APPROVAL

DATE: 12/23/2010

CC: Lisa Skarupa, Don Henry, Hari Sarkar, Sarah Pope Miksinski, Rik Lostritto, Brenda Gehrke, Leigh Verbois, Geoffrey Kim, Katherine DeLorenzo, Ellen Maher

Outstanding NDA Update Requests

AZ agreed to the following eight changes to the NDA and agreed to update the NDA prior to the 07-JAN-2011 PDUFA date:

1. Detailed process descriptions, including the revised design space, and revised process flow diagrams for both the drug substance and drug product
2. Drug product specification reflecting the new dissolution method and criterion
3. Analytical procedures reflecting the new dissolution method
4. Validation of analytical procedures reflecting the new dissolution method
5. Annual stability batch testing schedule
6. Container labels with revised established name – (vandetanib) tablets
7. Withdrawal of the proposed vandetanib tablet dissolution model
8. Withdrawal of the concurrent validation protocol and amended protocols for the drug substance site changes for manufacturing and (b) (4) protocols to CBE 30 reporting categories

Evaluation: Adequate – The sponsor updated all relevant sections of the NDA as requested, except container labels, in the 17-DEC-2010 Quality Amendment. The sponsor updated the container labels in the 20-DEC-2010 Amendment (see Attachment 1) as requested. With these submissions, the sponsor has fulfilled all outstanding NDA update requests.

Outstanding Information Request – Limit for (b) (4) in Povidone Excipient

During the pre-approval inspection on 01-Dec-2010 to 03-Dec-2010 at iPR, Canovanas, Puerto Rico, it has been noted (b) (4)

(b) (4) The Agency discussed this (b) (4) issue in a Telecon with AstraZeneca on 14-Dec-2010. AstraZeneca provided email response on 17-Dec-2010, and later submitted the response as SD 44 on 22- Dec-2010.

Facility Inspections

OC provided an overall recommendation of acceptable for all facilities associated with vandetanib 100 mg and 300 mg strength tablets on 15-DEC-2010 (see Attachment 2).

Evaluation: Adequate.

Overall Recommendation

Based on the satisfactory resolution of the outstanding CMC issues and the acceptable facility inspections recommendation, we recommend approval of NDA 22-405 vandetanib 100 mg and 300 mg strength tablets, pending labeling, from a CMC perspective.

Wendy I. Wilson-Lee

Wendy I. Wilson-Lee, Ph.D.
Review Chemist
ONDQA DPA-I

Debasis Ghosh

Debasis Ghosh, Ph.D.
Review Chemist
ONDQA DPA-II

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/s/

WENDY I WILSON
12/23/2010

DEBASIS GHOSH
12/23/2010

SARAH P MIKSINSKI
12/23/2010

NDA 22405

**Vandetanib Tablets
100 mg and 300 mg**

**iPR Pharmaceuticals, Inc
AstraZeneca Pharmaceuticals, LLP**

Debasis Ghosh, M. Pharm., Ph.D.

**Review of Drug Substance CMC
Division of Drug and Oncology Products**

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1. NDA 22405
2. REVIEW # 1
3. REVIEW DATE: 07-Dec-2010
4. REVIEWER: Debasis Ghosh, M. Pharm., Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 60042	16-Mar-2000
NDA (b) (4)	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Application/0000	07-Jul-2010
Response to Quality Information/0020	15-Oct-2010
Response to Quality Information/0034	23-Nov-2010
Response to Quality Information/0036	30-Nov-2010

7. NAME & ADDRESS OF APPLICANT:

Name: iPR Pharmaceuticals, Inc
 Address: PO Box 1624, Canovanas, Puerto Rico 00729-1624
 Representative: Debra N. Shiozawa
 Telephone: 787-875-1400

Authorized US Agent:
 Debra N. Shiozawa, Ph.D
 Director, Regulatory Affairs
 AstraZeneca Pharmaceuticals LP

Chemistry Review Data Sheet

1800 Concord Pike
PO Box 8355
Wilmington DE 19803
800-456-3669
Fax: 302-886-2822

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Vandetanib
c) Code Name/# (ONDC only): NA
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

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

10. PHARMACOL. CATEGORY: Anticancer

11. DOSAGE FORM: Immediate Release Tablet

12. STRENGTH/POTENCY: 100 mg and 300 mg per tablet

13. ROUTE OF ADMINISTRATION: Oral

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

SPOTS product – Form Completed

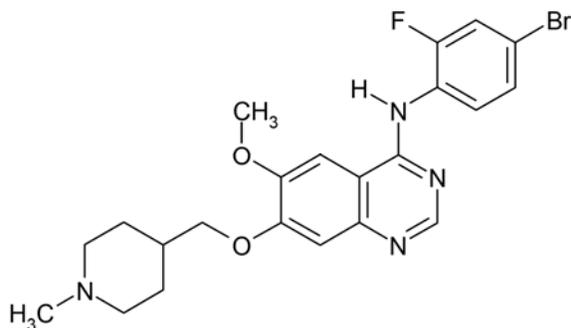
Not a SPOTS product

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

Chemistry Review Data Sheet

Chemical Name:

N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinazolin-4-amine

Structural Formula, Molecular Formula, Molecular Weight:**Molecular formula**

C₂₂H₂₄BrFN₄O₂

Relative molecular mass

475.36

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: [See Drug Product review](#)

B. Other Documents: [See Drug Product review](#)

18. STATUS: [See Drug Product review](#)

The Chemistry Review for NDA 22405

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the perspective of CMC-Drug Substance, the application is recommended to be approved.

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

No drug substance related issues.

II. Summary of Chemistry Assessments

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

Drug Substance:

The drug substance, Vandetanib, is a new molecular entity. It has a molecular formula of $C_{22}H_{24}BrFN_4O_2$ and molecular mass of 475.36. It has two pK_a values: (b) (4)

It is practically insoluble in water or basic pH but soluble in acidic pH. It is considered as BCS Class II. (b) (4)

Vandetanib is manufactured from (b) (4)

The applicant followed a Quality-by-design (QbD) approach for the development of Vandetanib drug substance. Consistent with the principles of ICHQ8 *Pharmaceutical Development* and ICHQ9 *Quality Risk Management*, the applicant identified the critical quality attributes (CQAs) and quality target product profiles (QTPPs). Based on the understanding of CQAs, a risk assessment study was performed to identify the most important material attributes and process parameters which affect the CQAs. The applicant employed Design of Experiments (DoEs) to understand the interaction of those material attributes and process parameters and proposed a design space in accordance with the concepts of ICHQ8. The applicant proposed number of control strategies based on historical batch data, manufacturing experience, and DoEs and also employed the concepts and principles of ICHQ10 *Pharmaceutical Quality System*.

Executive Summary Section

It is known that working within the design space ensures the production of acceptable grade of drug substance. The applicant indicated that all movements within the design space will be continuously assessed using ICHQ9 concepts and principles. Any proposed change of process parameters or material attributes will be evaluated to understand the potential risk as well as the co-ordinates of such changes with respect to design space boundaries.

The applicant provided a wide array of experimental and scientific understanding of each synthetic step, respective material attributes and process parameters and how it affects CQAs. The practical investigation performed during the development is extensive and informative. The proposed design space and control strategies for Vandetanib drug substance is acceptable.

The proposed **re-test period of** (b) (4) when stored at the recommended container closure system (protected from light) at ambient storage conditions is granted.

B. Description of How the Drug Product is Intended to be Used
[See Drug Product review](#)

C. Basis for Approvability or Not-Approval Recommendation
[See Drug Product review](#)
[See List of Drug Substance Deficiencies at the end of this document.](#)

III. Administrative

A. Reviewer's Signature

Debasis Ghosh, M. Pharm., Ph.D., CMC Reviewer, Div 1, Branch II, ONDQA

B. Endorsement Block

Sarah Pope Miksinski, Ph.D., Branch Chief, Div 1, Branch II, ONDQA

C. CC Block entered electronically in DARRTS

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/s/

DEBASIS GHOSH
12/07/2010

RICHARD T LOSTRITTO
12/07/2010

NDA 22-405

**Vandetanib Tablets
100 mg and 300 mg**

**iPR Pharmaceuticals, Inc
c/o AstraZeneca Pharmaceuticals LP**

**Wendy I. Wilson-Lee, Ph. D.
Office of New Drug Quality Assessment
for the
Division of Drug Oncology Products**

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Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA: 22-405
2. REVIEW: 01
3. REVIEW DATE: 07-DEC-2010
4. REVIEWER: Wendy I. Wilson-Lee, Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents

None.

Document Date

N/A

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment
Amendment
Amendment
Amendment
Amendment
Original Submission

Document Date

30-NOV-2010
23-NOV-2010
18-NOV-2010
03-NOV-2010
15-OCT-2010
07-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name: iPR Pharmaceuticals, Inc.

Address: PO Box 1624, Canovanas, Puerto Rico 00729-1624

Representative: Debra N. Shiozawa, Ph.D.
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals LP (Authorized US Agent)
1800 Concord Pike
Wilmington, DE 19803-8355

Telephone: 800-456-3669 (p)
302-886-2822 (f)

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name:
- b) Non-Proprietary Name (USAN):
- c) Code Name/# (ONDQA only):
- d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
 - Submission Priority: P

(b) (4)

Vandetanib
ZD6474

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)
10. PHARMACOL. CATEGORY: Treatment of locally advanced or medullary thyroid cancer

Chemistry Review Data Sheet

11. DOSAGE FORM: Tablets, Film-Coated
12. STRENGTH/POTENCY: 100 mg, 300 mg
13. ROUTE OF ADMINISTRATION: Oral
14. Rx/OTC DISPENSED: Rx OTC

15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

SPOTS product – Form Completed

Not a SPOTS product

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

Chemical Name: N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4-piperidinyl)methoxy]quinazolin-4-amine
Mol. Formula: C₂₂H₂₄BrFN₄O₂
Mol. Weight: 475.36

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	IV		(b) (4)	1	Adequate.	26-OCT-2010	(b) (4)
	III		7	N/A	04-NOV-2010		
	III		4	N/A			
	III		4	N/A			
	III		7	N/A	04-NOV-2010		
	III		7	N/A	04-NOV-2010		
	III		4	N/A			
	III		7	N/A	04-NOV-2010		

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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,042	Vandetanib for the treatment of solid tumors
NDA		(b) (4)

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending.		S. Chattopadhyay
EES	Pending.		OC
Pharm/Tox	Pending.		B. Gehrke
Biopharm	Pending.		Y. Moon
LNC	N/A	-	-
Methods Validation	Validation by FDA labs not needed.	10-NOV-2010	D. Ghosh & W. Wilson-Lee
DMEPA	Zictifa trade name not accepted.	07-OCT-2010	D. Baugh
EA	Categorical exclusion granted.	10-NOV-2010	D. Ghosh & W. Wilson-Lee
Microbiology	N/A	N/A	N/A

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Chemistry Review for NDA 22-405**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

We recommend a complete response action for vandetanib 100 mg and 300 mg tablets from a CMC perspective. The facilities inspection is incomplete and the sponsor has several outstanding commitments to provide updates to the NDA. We communicated our deficiencies to the sponsor in information requests on 15-SEP-2010, 27-OCT-2010, 04-NOV-2010, and 03-DEC-2010. AZ agreed to the following eight changes to the NDA and agreed to update the NDA prior to the 07-JAN-2011 PDUFA date:

1. Detailed process descriptions, including the revised design space, and revised process flow diagrams for both the drug substance and drug product
2. Drug product specification reflecting the new dissolution method and criterion
3. Analytical procedures reflecting the new dissolution method
4. Validation of analytical procedures reflecting the new dissolution method
5. Annual stability batch testing schedule
6. Container labels with revised established name – (vandetanib) tablets
7. Withdrawal of the proposed vandetanib tablet dissolution model
8. Withdrawal of the concurrent validation protocol and amended protocols for the drug substance site changes for manufacturing and (b) (4) protocols to CBE 30 reporting categories

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

We have no CMC Phase IV commitments at this time.

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s)**

Vandetanib tablets are an immediate-release, film-coated tablet available in two strengths – 100 mg and 300 mg. The 100 mg tablet is an 8.5 mm, round, biconvex, white, film-coated tablet with “Z100” debossed on one side and no debossing on the other side. The 300 mg tablet is a 16.0 mm length by 8.5 mm width, oval-shaped, biconvex, white, film-coated tablet with “Z300” debossed on one side and no debossing on the other side. The inactive ingredients in the vandetanib tablet core are dicalcium phosphate dihydrate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate. The tablet film-coat consists of hypromellose 2910, polyethylene glycol 300, and titanium dioxide.

The drug product manufacturing is (b) (4)

The tablet strengths differ in tablet weight. The sponsor employed a risk-based, QbD approach to the development of vandetanib tablets. AstraZeneca (AZ) defined a quality target product profile (QTPP) along with critical quality attributes (CQAs) for the drug product. Risk assessment processes used throughout development defined the investigations

Executive Summary Section

performed to gain a thorough understanding of vandetanib tablets. The investigations covered a wide range of input and material attributes as well as process parameters and led to a clear understanding of the relationships between, and impact of, the parameters investigated on the CQAs. AZ used this understanding to define a vandetanib tablet design space and control strategy that ensures delivery drug product that consistently meets the required quality.

The drug product quality is controlled through the control strategy, based on appropriate in-process controls and final product specification. The drug product specification includes tests and acceptance criteria for appearance, identification (UV, HPLC), single-point dissolution (model), assay (HPLC), and uniformity of dosage forms (in-process weight variation). All analytical procedures are appropriately validated for their intended use. The commercial packaging is 30-count HDPE bottles. AstraZeneca proposes a 36 month expiry for this product when stored in the commercial packaging at 25°C (77°F); excursions permitted to 15-30°C (59-86°F). Based on the stability data provided and in accordance with ICH Q1E, we grant a 36 month expiry for the 100 mg and 300 mg strength vandetanib tablets packaged in the commercial configuration and stored at USP controlled room temperature.

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

Vandetanib tablets are indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. The daily recommended dose of vandetanib is 300 mg once daily, with or without food. Patients who experience significant adverse events or toxicities may have their dose reduced to 200 mg (two, 100 mg tablets) or 100 mg vandetanib daily. For patients unable to swallow solids, administration of vandetanib may occur via an oral dispersion compounded by dissolving vandetanib tablets in 2 oz. of non-carbonated water with stirring for 10 minutes. Immediate dosing of the dispersion is recommended. Any residues in the glass should be mixed again with an additional half a glass (4 oz.) of non-carbonated water and swallowed. Administration of the dispersion may also occur through nasogastric or gastrostomy tubes. Vandetanib tablets are supplied in 30-count HDPE bottles.

C. Basis for Approvability or Not-Approval Recommendation

We recommend a complete response action for vandetanib 100 mg and 300 mg tablets from a CMC perspective. The facilities inspection is incomplete and the sponsor has several outstanding commitments to provide updates to the NDA. We communicated our deficiencies to the sponsor in information requests on 15-SEP-2010, 27-OCT-2010, 04-NOV-2010, and 03-DEC-2010. AZ agreed to changes to the NDA and agreed to update the NDA prior to the 07-JAN-2011 PDUFA date.

III. Administrative

A. Reviewer's Signature

Wendy I. Wilson-Lee

B. Endorsement Block

WWilson-Lee: 07-DEC-2010
SMiksinski: 07-DEC-2010

C. CC Block

DHenry
RLostritto
SChatterjee
CMoore
LSkarupa
EMaher

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/s/

WENDY I WILSON
12/06/2010

SARAH P MIKSINSKI
12/07/2010

Date: 08-Sep-2010

To: NDA 22405

From: Debasis Ghosh, M. Pharm., Ph.D.

Through: Christine Moore, Ph.D.

Subject: Considerations for Inspection for drug substance manufacturing process

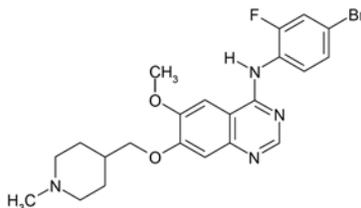
The application (NDA 22405) was submitted under 505(b)(1) by iPR Pharmaceuticals, Inc., a subsidiary of AstraZeneca Pharmaceuticals LP on 07-Jul-2010 to the Division of Drug and Oncology products for the commercialization of Vandetanib (Zictifa - the proposed proprietary name) tablets (100 mg and 300 mg) for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer. The application has recently received priority status and PDUFA date is 07-Jan-2011.

The purpose of this memo is to provide:

1. A brief overview of drug substance manufacturing process
2. A brief summary of QbD approaches as per ICHQ8 and ICHQ9
3. A brief summary of Reviewer's Assessment of Risk
4. CMC Considerations for Inspection (CFI)

Drug Substance:

Vandetanib has the following structure, molecular formula and molecular weight.



Molecular Formula: C₂₂H₂₄BrN₄O₂

Mol Wt: 475.36

It exists as a powder and exhibits low aqueous solubility.

(b) (4)

Manufacturing:

The applicant provided lists of names and addresses and responsibilities for the manufacturers of drug substance in Appendix I.

(b) (4)

The manufacturing process is

(b) (4)

A summary of potential impact of each Vandetanib stage on the individual CQAs is provided. The applicant stated that manufacturing experience and extensive multifactorial experimental designs were used to assess the risk of Vandetanib CQAs:

Based on the information from the development of synthetic process, risk assessment of each stage, and extensive systemically designed multifactorial studies, the applicant presented the design space as a relationship between the process inputs (material attributes and process parameters) and CQAs.

Reviewer's Assessment of Risk:

- No specific product or process related risks were identified. However, the applicant has proposed a quality by design approach including design space. The quality system should be suitable to evaluate the changes afforded by movement within a design space. Of special note, the starting material attributes are part of the design space, any change of supplier, synthesis and impurity profile of the starting materials could influence the quality of drug substance.

CMC Perspective Considerations for Inspection:

As a part of our commitment to share QbD information across offices, the CMC review team submits the following risk items for drug substance synthesis for consideration while on inspection:

- To ensure the movement within the design space, the following material attributes and process parameters should conform to the ranges listed in the Master batch record:

- The application includes a design space for drug substance synthesis. Typically plans for handling movements within/outside the design space are documented in the firm's Quality System (QS). In particular movements to areas of design space

- previously unverified at commercial scale should result in more detailed evaluation of risks to product quality.
- Starting material attributes are a component of the overall control strategy. Hence, the firm's QS should include a risk based approach for selection of raw material suppliers.

The CMC reviewer would like to participate in PAI and to share their knowledge with the investigator prior to and during the inspection. If you have any question, please contact Debasis Ghosh, Ph.D. (debasis.ghosh@fda.hhs.gov or at 301-796-4093).

Debasis Ghosh
WO 21/1619
ONDQA/Div I/Br II

Appendix I:

List of Names and Addresses and Responsibilities for the Manufacturers of Vandetanib

Name and address	Responsibility
(b) (4)	Manufacture Testing (except particle size) Release Stability testing
AstraZeneca UK Limited Silk Road Business Park Macclesfield Cheshire SK10 2NA UK	(b) (4) Packing Testing (b) (4) Release Stability testing

(b) (4)

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/s/

DON L HENRY
10/12/2010
Entered for Debasis Ghosh

SARAH P MIKSINSKI
10/15/2010

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
8.	<p>Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

9.	<p>Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	X		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	X		

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	Yes	No	Comment
11.	Has an environmental assessment report or categorical exclusion been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	X		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	X		
14.	Does the section contain information regarding the characterization of the DS?	X		
15.	Does the section contain controls for the DS?	X		
16.	Has stability data and analysis been provided for the drug substance?	X		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?	X		
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

E. DRUG PRODUCT (DP)				
	Parameter	Ye s	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	X		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	X		
21.	Is there a batch production record and a proposed master batch record?	X		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	X		
23.	Have any biowaivers been requested?		X	Confirm with John Duan on 8/17/10
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	X		
25.	Does the section contain controls of the final drug product?	X		
26.	Has stability data and analysis been provided to support the requested expiration date?			Information appears to support at least commercially viable shelf life (1 year). Proposed shelf-life is a Review issue
27.	Does the application contain Quality by Design (QbD) information regarding the DP?	X		
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		X	

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	X		

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?	X		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	X		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	[REDACTED]	(b) (4)	02-Oct-2008	
	III		25-Apr-2010		
	III		25-Aug-2010		
	III		26-Apr-2010		
	III		27-Jul-2009		
	III		22-Jul-2009		
	III		07-Oct-2008		
	III		28-Jul;-2009		
	III		13-Jun-2008		
			27-Apr-2010		
	III		03-May-2010		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

(b) (4)	III	(b) (4)		14-Apr-2010	
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I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	X		
33.	Have the immediate container and carton labels been provided?	X		

**PRODUCT QUALITY (Small Molecule)
FILING REVIEW FOR NDA or Supplement (ONDQA)**

J. FILING CONCLUSION				
	Parameter	Yes	No	Comment
34.	IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?			
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		Describe filing issues here or on additional sheets
36.	Are there any potential review issues to be forwarded to the Applicant for the 74-day letter?		X	Describe potential review issues here or on additional sheets

Haripada Sarker

8/25/2010

Name of
Pharmaceutical Assessment Lead or CMC Lead / ~~CMC Reviewer~~
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

Date

Sarah Pope Miksinski

8/25/2010

Name of
Branch Chief
Division of Pre-Marketing Assessment #1
Office of New Drug Quality Assessment

Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22405	ORIG-1	IPR PHARMACEUTICA LS INC	Zictifa (Vandetanib)

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/s/

HARIPADA SARKER
08/25/2010

SARAH P MIKSINSKI
08/25/2010

**Initial Quality Assessment
Branch V
Pre-Marketing Assessment Division III
Office of New Drug Quality Assessment**

OND Division: Division of Drug Oncology Products
NDA: 22-405
Applicant: IPR Pharmaceuticals, Inc. Puerto Rico
Authorizing US Agent: Debra N. Shiozawa, PhD
Director, Regulatory Affairs
AstraZeneca Pharmaceuticals LP
1800 Concord Pike
PO Box 8355
Wilmington DE
Letter Date: 7 July, 2010
Stamp Date: 7 July, 2010
PDUFA Goal Date: 7 December, 2010 (standard)
Trade name: Zictifa™ (proposed)
Established Name: Vandetanib
Dosage Form/Strength: Tablet (100mg and 300mg)
Route of Administration: Oral
Indication: ZICTIFA is indicated for the treatment of patients with unresectable locally advanced or metastatic medullary thyroid cancer.

Regulatory Filing For 505 (b) (1)
Related IND/NDA/DMF (Form IND 60,042; NDA (b) (4) DMFs (b) (4)
356h)

Assessed by: Haripada Sarker

Yes No

ONDQA Fileability: x

Comments for 74-Day Letter: x

Background Summary

Previous History

This NDA 22-405 was previously submitted to the Agency under NDA (b) (4). The IQA of NDA (b) (4) was reviewed by this author (see IQA in DARRTS under NDA (b) (4) by Haripada Sarker dated 8/27/2009). The primary reviewers of NDA (b) (4) were Ravi Kasliwal and Debasis Ghosh along with the involvement of Quality by Design (QbD) group in ONDQA. After initial review of the NDA (b) (4) the review team composed a list of information request (IR) intended to be conveyed to the applicant (see DARRTS under NDA (b) (4) dated 12/11/2009 by Sharmista Chatterjee). (b) (4)

Current Background

This NDA introduces ZICTIFA (Vandetanib), an immediate release tablet for oral administration containing 100 mg of drug substance. In the previous NDA (b) (4) the drug product proprietary name was indicated to be Zictifa™ (Vandetanib). Vandetanib, the drug substance, is a new molecular entity. The NDA is submitted by AstraZeneca (AZ) on behalf of IPR Pharmaceuticals, Inc. In the application, (b) (4) 100 and 300 mg tablet strengths were developed, and data from both strengths are included in this NDA. (b) (4)

AstraZeneca adopted Quality by Design (QbD) approach to develop Zactima. AZ has employed a structured, systematic approach to the development of both vandetanib (drug substance) and Zactima tablets (drug product). The Applicant states that a Quality Risk Management approach (ICH Q9) has been integral to the development process and that risk assessment processes have been used throughout development for both drug substance and drug product. As an overall outcome of this approach, AZ claims that a thorough understanding has been gained for vandetanib and Zactima tablets; in terms of the attributes of both the drug substance and drug product (per ICH Q8) and their respective manufacturing processes.

Applicant submitted this NDA under the ONDQA pilot program for the New Pharmaceutical Quality Assessment System (NPQAS). Between 9/11/2005 and 1/16/2007, several CMC communications took place between AZ and FDA related to the participation of AZ in the pilot program and for the proposed Quality-by-Design (QbD) approach. Reference is also made to Module 1.2, in which key FDA interactions (IND 60,042) during the development of vandetanib are described. The following are some of the key interactions related to CMC.

- September 28, 2005, End of Phase II briefing package submitted, which included proposed registered starting materials, bioequivalence strategy, drug product stability package, and a (b) (4)
- April 12, 2006, AZ requested a meeting on 15 June 2006 with the FDA under the Pilot Program to discuss AZ approach to Design Space to be included in the CMC sections of the NDA. Reference is made to Type C meeting on June 15, 2006 (DARRTS reference: FDA communication date 7/14/2006), which is another follow-up meeting to the January 17, 2006 meeting regarding participation in the CMC pilot program for vandetanib tablets.

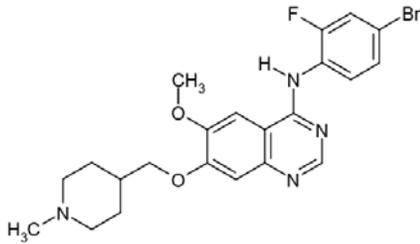
- December 20, 2006, AZ submitted Briefing Document describing proposed strategy for control of potential genotoxic impurities.
- January 16, 2007, AZ submitted Briefing package for pre-NDA meeting on February 1, 2007. Reference is made to pre-NDA Type C CMC meeting package (FDA received date 1/16/2007, supporting document #545) for t-con meeting date 2/1/2007 to discuss further regarding CMC pilot program. FDA written response was communicated by project manager, Amy E. Bertha on 1/31/2007 (see DARRTS). Minutes for these meetings should be examined by the reviewer.

This NDA includes updates on DS and DP stability data along with other minor CMC changes.

Drug Substance (DS)

The drug substance, Vandetanib is an off-white powder, and exhibits pH dependent aqueous solubility. The DS is defined as 'low solubility' under the Biopharmaceutics Classification System (BCS). (b) (4)

The chemical structure of Vandetanib is below



The manufacturing process is (b) (4)

Manufacture, Testing (b) (4), Release and Stability testing are performed at:

(b) (4)

Testing [REDACTED] (b) (4), Release and Stability testing are performed at:
AstraZeneca UK Limited
Silk Road Business Park
Macclesfield
Cheshire
SK10 2NA
UK

A QbD approach was utilized to develop and optimize the manufacturing process for Vandetanib. The Critical Quality Attributes (CQAs) and Quality Attributes (QAs) were identified for the production of a drug substance suitable for formulation into the desired drug product. The Drug Substance CQAs are listed as identity by IR or NIR, polymorphic form, content by HPLC, drug-related impurities (including named impurities and genotoxic impurities content), volatile impurities, particle size, residual solvents, water content by Karl Fischer, description, metal content, and microbial purity.

The design space has been proposed using a combination of prior knowledge and experimentation in conjunction with science-based risk management processes. For each stage, the acceptable ranges and relationship of process parameters (including solvents, reagents, reaction quantities, temperature and time) and the CQAs of vandetanib have been documented in master batch records.

The proposed design space for vandetanib is applied to the following areas:

- (a) The specification for vandetanib representing the quality attributes needed to assure the safety and efficacy of Vandetanib DP.

[REDACTED] (b) (4)

- (c) The specifications for the starting materials.

- (d) The specification for [REDACTED] (b) (4)

- (e) Description of the manufacturing processes for [REDACTED] (b) (4) which includes necessary in-process controls and process parameters.

ICH primary stability studies were conducted on three batches ME/1, ME/2 and ME/3, manufactured by AstraZeneca, Macclesfield, UK, according to the current production process at the production scale, and are currently being evaluated in a 60 month primary stability study. The study is ongoing and the latest timepoint is 24 months. Supporting stability data were generated using batch C6/6 manufactured at [REDACTED] (b) (4) using the current production process at the production scale, and in facilities proposed for commercial manufacture. Following Table 1 includes the current stability data profiles of DS.

Table 1. Storage conditions and sampling protocol for stability studies

Storage condition	Temperature/ Humidity	Packaging	Sampling timepoints (months)	
			ICH primary stability study	Production scale stability study
(b) (4)				

^a Optional.

^b The need for testing will be evaluated on the basis of data from earlier timepoints. Testing will be continued to include the proposed retest period.

^c Batch ME/1 only for ICH primary study.

^d [Redacted] (b) (4)

RH Relative humidity.

AH Ambient humidity.

Stability specifications include Description, Assay by HPLC, Organic impurities by HPLC, Method 1, Organic impurities by HPLC, Method 2, Water content by Karl Fischer, [Redacted] (b) (4)

[Redacted] Based on DS stability data a retest period of [Redacted] (b) (4) for vandetanib DS is proposed when stored in the primary packaging at controlled room temperature (20°C to 25°C, 68°F to 77°F), protected from light.

Drug Product (DP)

ZICTIFA (Vandetanib) drug product information includes 2 tablet strengths containing 100 and 300 mg of vandetanib respectively. The 100 mg strength is presented as a round, biconvex, white, film-coated tablet with a diameter of approximately 8.5 mm. ‘Z100’ is impressed on one side; the other side is plain. The 300 mg strength is presented as an oval-shaped, biconvex, white, film-coated tablet with a length of approximately 16.0 mm and. (b) (4)

Following is the component and composition of DP (Table 2). The tablets are distinguished by size, shape and impression (Z100 and Z300).

Table 2. DP Component and Composition

Ingredients	100 mg		300 mg	
	Amount per tablet		Amount per tablet	
	Amount (mg)	Amount (% of tablet core)	Amount (mg)	Amount (% of tablet core)
Tablet core				
Vandetanib	100.0	(b) (4)	300.0	(b) (4)
Dibasic calcium phosphate dihydrate ^a				(b) (4)
Microcrystalline cellulose				
Crospovidone				
Povidone				
Magnesium stearate				
(b) (4)				
Core tablet weight (mg)				
Tablet coating				
Hypromellose 2910 ^{c, d}				(b) (4)
Polyethylene glycol 300 ^{c, e}				
Titanium dioxide ^c				
(b) (4)				
Nominal coated tablet weight (mg)				

The batch size of Vandetanib tablets will be in the range (b) (4)

Above Table presents the upper and lower limits of the batch formulae justified as part of the Vandetanib tablets design space.

The tablets are produced using a conventional manufacturing process involving (b) (4)

The proposed DP manufacturing site is as following;
 IPR Pharmaceuticals Inc.
 Street 188, Lot 17
 San Isidro Industrial Park
 Canovanas 00729
 Puerto Rico

Control of Critical Steps: The Vandetanib tablets proposed design space mainly consists of boundaries for formulation and intermediate product attributes. Although intermediate product attributes are considered to be independent of scale and equipment, ranges for these factors have been included in the design space. Site of drug product manufacture is constrained because of regulatory and GMP

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22405	ORIG-1	IPR PHARMACEUTICA LS INC	Zictifa (Vandetanib)

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/s/

HARIPADA SARKER
08/05/2010

WILLIAM M ADAMS
08/05/2010
William Adams, acting for Sarah Pope Miksinski