

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022433Orig1s000

CHEMISTRY REVIEW(S)

CHEMICAL MANUFACTURING CONTROLS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 22-433	Applicant: AstraZeneca	Stamp Date: 16-NOV-2009
Drug Name: Ticagrelor	NDA Type: Priority	Filing Meeting: 17-DEC-09

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

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?			Consult: Raanan Bloom, OPS/PARS, 14-DEC-09
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	NA		

IS THE CMC SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. **NA**

Chhagan G. Tele, Ph.D.	17-DEC-09
Reviewing Chemist (Drug Substance), DPA 1, ONDQA	Date
Thomas Wong, Ph.D.	17-DEC-09
Reviewing Chemist (Drug Product), DPA 1, ONDQA	Date
Ramesh Sood, Ph.D.	17-DEC-09
Branch Chief, DPA 1, ONDQA	Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

CHHAGAN G TELE
12/17/2009
Filing memo

RAMESH K SOOD
12/17/2009

ONDQA Division Director's Memo
NDA 22-433, BRILINTA (ticagrelor) Tablets 90 mg
Date: 16-DEC-2010

Introduction

BRILINTA tablets are indicated for the prevention of thrombotic events in patients with acute coronary syndromes. ONDQA recommends APPROVAL.

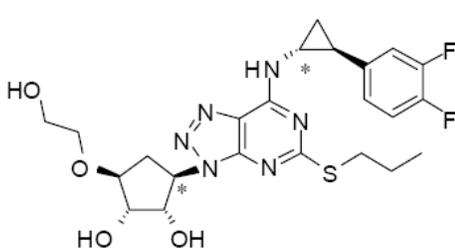
Administrative

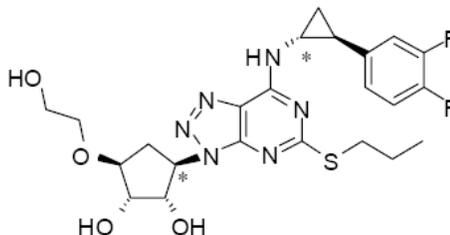
The original submission of this 505(b)(1) NDA was received 13-NOV-2009 from Astra Zeneca LP, Wilmington, DE. This is a standard (1S) NDA. In addition to the original submission; these two amendments were reviewed in May and July.

The application is supported by IND 65,808 and ten Drug master Files (DMFs).

All consults are acceptable. ONDQA recommends approval

Drug Substance (ticagrelor)

USAN (2007):	ticagrelor
Non-Proprietary Name:	(1S,2S,3R,5S)-3-[7-{[1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol
Chemical Formula:	C ₂₃ H ₂₈ F ₂ N ₆ O ₄ S
Molecular Weight:	522.57
CAS registry #:	274693-27-5
Structure:	



(b) (4)

Ticagrelor is a (b) (4) powder with a melting point 140-142° C (b) (4). The drug substance has low water solubility (0.016 mg/mL at 20 ±5° C). It does not exhibit pH dependent solubility in aqueous buffers.

Ticagrelor is a BCS Class 4 compound (low solubility, low permeability). There are (b) (4)

Four polymorphs have been identified and (b) (4) has been selected for development. This form has been used in all pre-clinical and clinical studies, and it does NOT convert to any other form on storage.

Ticagrelor is manufactured by a conventional (b) (4) scheme from (b) (4) starting materials as previously agreed (End-of-Phase II CMC briefing document dated 07-JUN-07, preliminary responses from the Agency, 10-SEP-07, and AstraZeneca response to the Agency comments, 04-OCT-07).

The applicant has employed some concepts and principles of Quality by Design (QbD) approach to the development of the ticagrelor (b) (4) and manufacturing process.

Drug Product (BRILINTA) tablets 90 mg

The drug product is an immediate release film-coated tablet dosage form. The tablets are round, biconvex, yellow, film-coated tablets marked with a “90” above “T” on one side. The tablets contain 90 mg of ticagrelor and the following excipients:

mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate (b) (4) (b) (4) hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow.

Tablets are packaged in HDPE bottles with two different tablet counts per bottle, 60 tablets and 180 tablets. They are also packaged into 100 count hospital unit dose PVC blisters with one tablet per cavity. Tablets are stored at 25°C (77°F); with excursions permitted to 15°-30°C (59°- 86°F). The data supports a twenty-four (24) month expiration dating period for the tablets when packaged in the proposed commercial packages and stored in the aforementioned storage conditions.

Rik Lostritto, Ph.D., Director, ONDQA Division III

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/s/

RICHARD T LOSTRITTO
12/16/2010

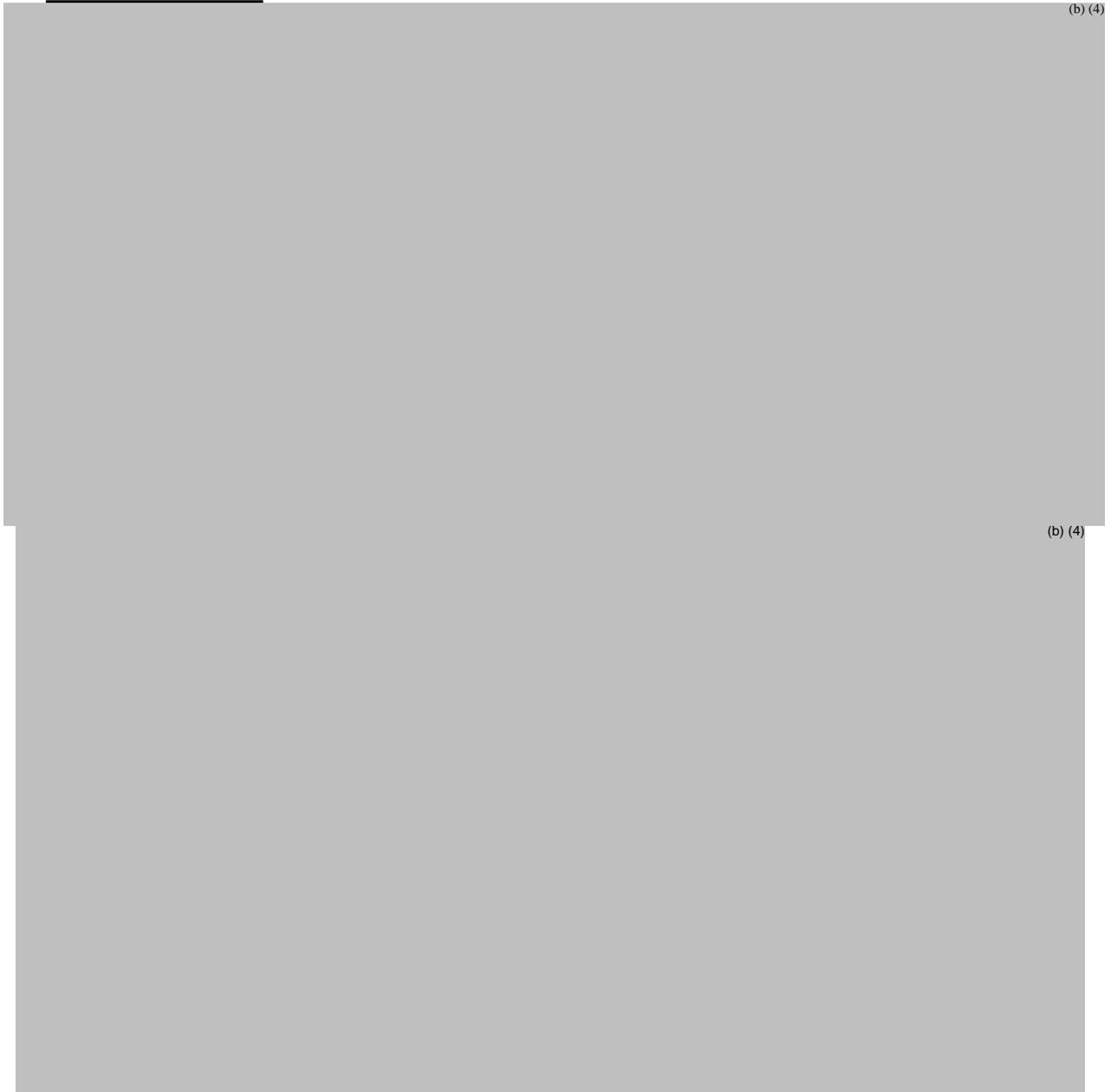
MEMORANDUM

Office of New Drug Quality Assessment

Division of Cardio-Renal Drug Products
Chemistry, Manufacturing, and Controls

DATE: 11-AUG-2010
TO: NDA 22-433 (Refer Review #1 in DARRTS, 23-JUL-2010)
FROM: Chhagan G. Tele, Ph.D. and Thomas Wong, Ph.D., CMC Reviewers,
ONDQA/Branch 1
SUBJECT: Final CMC Recommendation for NDA 22-433, (Brilinta™) Tablets

DRUG SUBSTANCE



(b) (4)

(b) (4)

(b) (4)
 The validation data demonstrated that the analytical procedure is suitable for its intended use.

3) Qualification of Impurities

Pharmtox reviewer (Dr. Elizabeth Hausner) indicated in her reviews (dated 23-JUN-10 and 10-AUG-10) that the individual identified impurities (b) (4) in the drug substance are qualified to the acceptance limits.

4) Office of Compliance (OC) Recommendation regarding the cGMP Inspections

The CDER Office of Compliance (OC) issued an overall "Acceptable" recommendation regarding the cGMP inspections for NDA 22-433 on 09-AUG-2010. A copy of the establishment evaluation report is attached (see Attachment 2 below).

DRUG PRODUCT Specification

Comment: A teleconference with the applicant was conducted on July 23 requesting the applicant to:

1. Identify an assay method to be used for analysis of quality post-release. We suggested that the primary method for ID test is NIR and for assay is HPLC.
2. Assign test method number to each of the test method and make reference to these method numbers in the drug product specification.
3. Modify the PQITs testing frequency from once per annum to at minimum once per annum.
4. Optionally, add a footnote to the PQITs table to indicate that the PQITs will also be performed when processes are changed (e.g. moving process parameters within or outside the design space boundaries) based upon risk assessment.
5. Revise footnote (a) to clarify the (b) (4).

Applicant's response on July 26, 2010 (Amendment 0048):

The applicant mentioned that specification is updated to use HPLC as the primary method for both identification and assay, and NIR is an alternative test method for identification.

Below is the updated drug product specification:

Test procedure	Acceptance criteria	Method reference
Description	Round, biconvex, yellow, film-coated tablets, intagliated with 90 on 1 side and plain on the reverse	Visual, [CV.000-513-902]
Identification ^a	Positive identification confirmed	Primary method: HPLC/UV and UPLC/UV [CV.000-508-923] Alternative methods: NIR [CV.000-464-062]
Assay ^a	90% to 110% of label claim	Primary method: HPLC [CV.000-442-109] Alternative methods: NIR [CV.000-464-062] UPLC [CV.000-442-113]
Dissolution ^a	Shall comply with the requirements of the United States Pharmacopoeia: Q= (b) (4) at 45 minutes Q= at 60 minutes	Apparatus 2, 75 rpm, 900 mL, 0.2% Tween 80, UV measurement, [CV.000-519-756]
Uniformity of dosage units ^a	Shall comply with the requirements of the United States Pharmacopoeia	Uniformity of dosage units by weight variation, [CV.000-516-070]

^a (b) (4)
 HPLC High performance liquid chromatography.
 UPLC Ultra pressure liquid chromatography.
 NIR Near infrared.

PQITs for the ticagrelor film-coated tablets, 90 mg are presented below:

Test procedure	Acceptance criteria	Method reference	Testing frequency
Degradation products ^{a, b}	Shall comply with the following limits if tested:	Primary method: HPLC [CV.000-442-111]	At a minimum once per annum
Individual unspecified degradation products	NMT (b) (4)	Alternative method: UPLC [CV.000-442-113]	
Total degradation products	NMT		
^a	(b) (4)		
^b	The degradation products test will not normally be performed at release, however, all batches would pass the acceptance criteria, if tested.		
HPLC	High performance liquid chromatography.		
UPLC	Ultra pressure liquid chromatography.		

Comment: Response is acceptable. In the specification, the applicant has designated the primary methods for ID test and assay. The applicant has also included method numbers to all methods.

In the PQITs, the applicant has changed the testing frequency from once per annum to at a minimum once per annum. The applicant, however, did not add the optional footnote to the PQITs table to indicate that the PQITs will also be performed when processes are changed (e.g. moving process parameters within or outside the design space boundaries) based upon risk assessment. Since the footnote is optional, the commission of this footnote is acceptable. The footnote (a) has

LIST OF DEFICIENCIES TO BE COMMUNICATED TO THE APPLICANT

There are no outstanding deficiencies. Requests addressing issues have been satisfactorily answered by the applicant and the responses are acceptable.

Recommendation: From a CMC perspective, the application is recommended for the Approval of NDA 22-433.

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page.

Attachment 2

NDA 22-433: Overall Acceptable Recommendation from the CDER Office of Compliance

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

Application:	NDA 22433/000	Sponsor:	ASTRA USA
Org. Code:	110		1800 CONCORD PIKE
Priority:	1		WILMINGTON, DE 198038355
Stamp Date:		Brand Name:	AZD6140
PDUFA Date:		Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	18-JUL-2010	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; TICAGRELOR; 90MG
Application:	NDA 22433/000	Sponsor:	ASTRA USA
Org. Code:	110		1800 CONCORD PIKE
Priority:	1		WILMINGTON, DE 198038355
Stamp Date:	16-NOV-2009	Brand Name:	AZD6140
PDUFA Date:	16-SEP-2010	Estab. Name:	
Action Goal:		Generic Name:	
District Goal:	18-JUL-2010	Product Number; Dosage Form; Ingredient; Strengths	001; TABLET; TICAGRELOR; 90MG
FDA Contacts:	D. HENRY	Project Manager	301-796-4227
	K. SRINIVASACHAR	Team Leader	301-796-1760

Overall Recommendation: ACCEPTABLE on 09-AUG-2010 by A. INYARD ()

Establishment:

(b) (4)

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE STABILITY TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-JUN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Establishment: CFN: 9610565 FEI: 3002806411
ASTRAZENECA
KVARNBERGAGATAN 12 (STRANGNASVAGEN 20)
SODERTALJE, , SWEDEN

DMF No: AADA:

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 2517100 FEI: 2517100
ASTRAZENECA PHARMACEUTICALS LP
587 OLD BALTIMORE PIKE
NEWARK, DE 197021307

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 03-DEC-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Establishment: CFN: 9615999 FEI: 3003342394
ASTRAZENECA SWEDEN OPERATIONS (TABLET PRODUCTION SWEDEN)
GARTUNAVAGAN
SODERTALJE, , SWEDEN

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 27-APR-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: (b) (4)

DMF No: **AADA:**

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

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

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: (b) (4) MANUFACTURER

Profile: [REDACTED] (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-AUG-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: [REDACTED] (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: [REDACTED] (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-FEB-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

Establishment: [REDACTED] (b) (4)

DMF No: [REDACTED] AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

Profile: [REDACTED] (b) (4) OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 18-DEC-2009

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

CHHAGAN G TELE

08/10/2010

CMC memo to NDA 22-433. Approval recommendation from the CMC perspectives.

THOMAS M WONG

08/11/2010

CHRISTINE M MOORE

08/12/2010

NDA 22-433

Brilinta[™] (ticagrelor) Tablets

AstraZeneca LP

Chhagan G. Tele, Ph.D.

Thomas M. Wong, Ph.D.

Division I/Branch 1

Office of New Drug Quality Assessment

**Division of Cardiovascular and Renal Products
Review of Chemistry, Manufacturing, and Controls**

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Chemistry Assessment Section

Chemistry Review Data Sheet

1. NDA: 22-433
2. REVIEW #: 1
3. REVIEW DATE: July 23, 2010
4. REVIEWER: Chhagan G. Tele, Ph.D. and Thomas M. Wong Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	13-NOV-2009
Amendment 0029 (Response to IR)	31-MAY-2010
Amendment #: 0046	16-JUL-2010

7. NAME & ADDRESS OF APPLICANT:

Name:	AstraZeneca LP
Address:	1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
Representative:	Emery Gigger, Regulatory Affairs Director 1800 Concord Pike P.O. Box 8355 Wilmington, DE 19803-8355
Telephone:	(302) 885-4048

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Brilinta™ (the proposed tradename)
- b) Non-Proprietary Name/USAN: ticagrelor
- c) Code Name/# (ONDQA only): AZD6140, AR-C126532XX
- d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 1
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(1); Brilinta™ (ticagrelor) Tablets (90 mg Strength)

Chemistry Assessment Section

10. PHARMACOL. CATEGORY: For the prevention of thrombotic events in patients with acute coronary syndromes
11. DOSAGE FORM: Tablets
12. STRENGTH/POTENCY: 90 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:

USAN (2007): ticagrelor

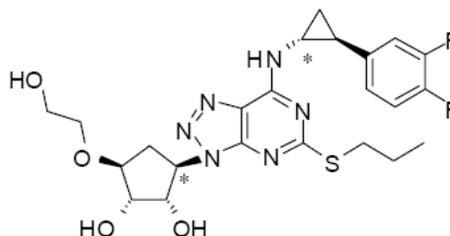
Non-Proprietary Name: (1S,2S,3R,5S)-3-[7-{[1R,2S)-2-(3,4-Difluorophenyl)cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3] triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

Chemical Formula: $C_{23}H_{28}F_2N_6O_4S$

Molecular Weight: 522.57

CAS registry #: 274693-27-5

Structure:



(b) (4)

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)	(b) (4)	4			Sufficient information in application.

Assessment Section
(b) (4)

(b) (4)	III	[REDACTED]	4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application
	III		4			Sufficient information in application

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	65808 (effective 29-APR-2003) Tablets	For the reduction of atherosclerotic events in patients with acute coronary syndrome
DMF	[REDACTED] (b) (4)	

Chemistry Assessment Section

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	N/A	N/A
EES	Pending		Shawnte L. Adams (HFD-322)
Pharmtox	Pending		
Biopharm	Pending		
LNC	N/A		
Methods Validation	Methods are routine. No need to send to FDA labs for validation.		
DMETS	N/A		
EA	FONSI Recommended	07-MAR-10	Raanan Bloom
Microbiology	N/A	N/A	N/A

Chemistry Assessment Section

The Chemistry Review for NDA 22-433**The Executive Summary****I. Recommendations****A. Recommendation and Conclusion on Approvability**

NDA 22-433 for Brilinta™ (ticagrelor) Tablets can not be approved from the CMC standpoint due to the following pending issues:

1. [REDACTED] (b) (4)
2. The applicant needs to provide updated drug product specification.
3. The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.

Note: Pharmtox reviewer (Dr. Elizabeth Hausner) was consulted for the input whether the individual identified impurities [REDACTED] (b) (4) are qualified or not to the acceptance limits. Since Pharm tox review is in progress, we did not send any request to the sponsor about this issue. Batch analysis data of early and late development drug substance batches showed these impurities in the ranges of [REDACTED] (b) (4) respectively. These impurities did not increase on stability (at 12 months long term and 6 months accelerated storage conditions).

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

None as per this review

II. Summary of Chemistry Assessments**A. Description of the Drug Product(s) and drug substance(s)****Drug product**

The applicant has developed an immediate release film-coated tablet dosage form as an antithrombotic agent. It is indicated to reduce the rate of thrombotic events (including stent thrombosis) for patients with acute coronary syndromes who are to be managed medically or invasively with percutaneous coronary intervention and/or coronary artery bypass graft. The trade name for the ticagrelor tablet is BRILINTA™ and the tablets round, biconvex, yellow, film-coated tablets marked with a “90” above “T” on one side. The tablets contain 90 mg of ticagrelor and the following excipients: mannitol, dibasic calcium phosphate, sodium starch glycolate, hydroxypropyl cellulose, magnesium stearate, [REDACTED] (b) (4) hydroxypropyl methylcellulose, titanium dioxide, talc, polyethylene glycol 400, and ferric oxide yellow. Tablets are packaged in HDPE bottles with two different tablet counts per bottle, 60 tablets and 180 tablets. They are also packaged into 100 count hospital unit dose PVC blisters with one tablet per cavity. Tablets are stored at 25°C (77°F); with excursions permitted to 15°-30°C (59°- 86°F). Available 12 months stability data supports 24-month expiration dating period for the tablets when packaged in the proposed commercial packages and stored in the afore-mentioned storage conditions.

Drug substance

Ticagrelor (AZD6140), a new molecular entity, is the first of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines. Clinical development was carried out under IND 65,808 and the efficacy and safety of ticagrelor is derived mainly from Phase 3 study comparing this

Chemistry Assessment Section

drug with clopidogrel. Ticagrelor is a small molecule with molecular formula $C_{23}H_{28}F_2N_6O_4S$ and molecular weight 522.57. Ticagrelor is a (b) (4) powder with a melting point 140-142° C (DSC). The drug substance has low water solubility (0.016 mg/mL at 20 ±5° C). It does not exhibit pH dependent solubility in aqueous buffers. According to Biopharmaceutics Classification System (BCS), ticagrelor is classified as Class 4 compound (low solubility, low permeability).

Four (b) (4) polymorphs have been identified and (b) (4) has been selected for development. This form has been used in all pre-clinical and clinical studies and has been shown not to convert to any other form on storage. Ticagrelor is manufactured by a conventional (b) (4) scheme from (b) (4) designated starting materials. Designation of starting materials and final intermediates in the synthesis of ticagrelor was agreed (End-of-Phase II CMC briefing document dated 07-JUN-07, preliminary responses from the Agency, 10-SEP-07, and AstraZeneca response to the Agency comments, 04-OCT-07).

The drug substance, ticagrelor will be manufactured exclusively by AstraZeneca, Sodertarje in Sweden or (b) (4) for commercial use. The commercial batch size of the drug substance to be manufactured is (b) (4). The applicant provided adequate information regarding structure elucidation and confirmation, method of manufacture, in-process controls, test methods, container closure system, and stability testing of ticagrelor drug substance.

The applicant has employed some of the concepts and principles of Quality by Design (QbD) approach to the development of the ticagrelor (b) (4) route and manufacturing process. The boundaries of the ticagrelor design space have been risk assessed and investigated, and it has been shown that there is low risk of interactions of parameters affecting any of the ticagrelor critical quality attributes (CQAs). The control strategy constitute of those controls (in-process controls, starting material specifications, intermediate specifications as well as the manufacturing process) that are put in place to ensure that routine operation of the manufacturing process remains within the design space so that CQAs are delivered consistently. Following CQAs have been identified and risk assessment processes have been used to define the experimental work performed: Description, Identity, Assay, Absolute configuration, Organic impurities, Solvents, (b) (4) (b) (4), Polymorphic form, Particle size, Metals, and Microbiology.

A risk assessment has been performed based on the current process understanding and prior knowledge. Failure Mode, Effects and Criticality Analysis (FMECA) was used for risk assessments throughout the development. The output of the risk assessments was then used to prioritize further investigations of the parameters, design of experimental investigations, and provided an indication on what knowledge gaps/risks should be addressed and in which order. The results from the experimental work then updated the current process understanding, leading to the ticagrelor design space. Design space boundaries, consisting of a multi-dimensional combination of parameters (e.g. mol. equivalents of reagents, time and temperature) have been defined which allow CQAs like impurities to be within target values. Similarly, design space boundaries for polymorphic form, particle size and the genotoxic impurity (b) (4) have been defined. Comprehensive studies have been carried out to understand the potential impurities and degradation products which may be present in ticagrelor. In addition, a comprehensive risk based process has been used to ensure that the levels of potential genotoxic impurities present in the drug substance are below the Threshold of Toxicological Concern as defined in the EMEA guidance. Based on genotoxicity tests, the applicant controlled only one impurity (b) (4) in the drug substance.

Chemistry Assessment Section

The knowledge gained during development is based mainly on the analysis of laboratory experiments. Scale-up experiments, modeling of scale dependent parameters and scientific rationale have been used to investigate potential scale up effects. It is claimed that these assessments establish that data generated at laboratory scale can be considered representative for commercial scale manufacture and that no changes in ticagrelor quality result from changes in equipment and scale from laboratory to pilot plant and commercial scale. The control strategy for ticagrelor ensured that routine manufacture remained within the boundaries of the established design space and is based on the use of cGMP, specifications for starting materials and isolated intermediates, in-process controls, and drug substance specifications. A change management process is provided which includes an assessment whether the proposed change falls within, or is outside, the approved design space.

The specifications for drug substance included Description (Visual), Identification (IR), Assay (HPLC), Impurities (Organic impurities: HPLC and Residual solvents: GC), Potential genotoxic impurity^{(b) (4)} (HPLC), Particle size (Laser diffraction), Polymorphic form (XRPD), ^{(b) (4)}

^{(b) (4)} Validated analytical methods were provided in the submission.

Release data of 31 drug substance batches used in clinical trials, primary drug product stability studies, and manufacturing of registration batches is provided. No significant variations between the individual ticagrelor batches manufactured via the commercial process have been observed. Ticagrelor batches are consistent with respect to the analytical parameters tested. The content acceptance criteria of Ticagrelor (HPLC, 98-102%) is adequate. The specifications for the each specified impurities (^{(b) (4)} any individual unspecified impurity, ^{(b) (4)}), total organic impurities, ^{(b) (4)} are provided ^{(b) (4)}

The drug substance primary stability data included long and intermediate-term stability data for three batches (#s ^{(b) (4)}), representative of larger scale commercial production in a facility on the site where commercial manufacturing is proposed (AstraZeneca, Sodeltarje, stored 12 months at 25° C/60% RH, and 30° C/65% RH and 6 months at 40° C/75% RH). In addition, 3 months long-term data for third primary stability batch (SD/0853, ^{(b) (4)}) batch manufactured at another proposed commercial manufacturing site (^{(b) (4)}) have been provided as supporting data using the proposed commercial process (stored 3 months at 25° C/60% RH, and 30° C/65% RH and 40° C/75% RH). No significant change in description, assay, and impurities was observed after storage at 25° C/60% RH and 30° C/65% RH for 12 months or at 40° C/75% RH for 6 months. All results complied with the specification. The stability data demonstrated the chemical and physical stability of the drug substance. A re-test period of ^{(b) (4)} is granted for ticagrelor stored at or below 30° C in the primary packaging (protected from light).

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

The recommended initial dose is a single 180 mg oral loading dose (two – 90 mg tablets) and then continued at 90 mg twice daily. BRILINTA should be used in combination with aspirin. In chronic treatment, BRILINTA should be used with low dose aspirin (75-150 mg). BRILINTA can be administered with or without food.

Chemistry Assessment Section

C. Basis for Approvability or Not-Approval Recommendation

Adequate information has been provided to allow a satisfactory evaluation of the quality of both drug substance (DS) and drug product (DP). DS and DP manufactured and packaged in accordance with the procedures and proposed specifications to assure their quality throughout shelf life. From the CMC point of view NDA 22-433 for Brilinta™ (ticagrelor) Tablets can not be approved due to pending issues mentioned in Section I A above. Consult was sent to Raanan Bloom, OPS/PARS (14-DEC-09) by Mr. Don Henry (ONDQA PM) to evaluate the data submitted by the applicant for Environmental Assessment (EA) for ticagrelor. It is required to prepare an EA if the expected introduction concentration (EIC) to the aquatic environment is >1 ppb. Review of the Environmental Assessment (consult conclusion and recommendation, Raanan Bloom, 02-MAR-2010) concluded that no significant adverse environmental impacts are expected from the approval of this NDA. A Finding of No Significant Impact (FONSI) is recommended.

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

See electronic signatures in DAARTS.

B. Endorsement Block

Chemist Name:	Chhagan G. Tele, Ph.D., Thomas M. Wong, Ph.D.
Branch Chief Name:	Ramesh Sood, Ph.D.
Project Manager Name:	Michael Monteleone, Pharm.D.

C. CC Block

See DARRTS.

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Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS M WONG
07/23/2010

CHHAGAN G TELE
07/23/2010

CHRISTINE M MOORE
07/23/2010

Office of New Drug Quality Assessment

DATE: March 3, 2010
TO: NDA 22-433 Extended Review Team
FROM: Thomas M. Wong, Ph.D.
THROUGH: Christine Moore, Ph.D.
SUBJECT: Considerations for Inspection (CFI) of AstraZeneca for NDA 22-433 – Drug Product

NDA 22-433 was submitted by AstraZeneca LP for Brilinta™ (ticagrelor) 90 mg immediate release film-coated tablets. The proposed indication is for reduction of rate of thrombotic events (including stent thrombosis) in patients with acute coronary syndromes who are to be managed medically or invasively with percutaneous coronary intervention and/or coronary artery bypass graft. The following are the manufacturing sites for the drug product:

- AstraZeneca, Gartnavagan, Sodertalje, Sweden: CFN 9615999, drug product manufacturer, packager, QC, release, and stability
- [REDACTED] (b) (4) drug product stability testing

This memo includes an overview of the drug product manufacturing processes and findings from the CMC review. This NDA submission contained QbD information for the development of the drug product. The applicant used a combination of [REDACTED] (b) (4) approach to define scale-independent design space boundaries for each of the manufacturing unit operations. The findings described in Table 2 are for considerations by the Office of Compliance regarding pre-approval inspection.



There are no particular critical manufacturing steps mentioned. The following table (Table 1) describes the critical parameters for each unit operation as specified in the design space and the in-process control limits.

Table 1

Unit operation	Design space boundary	In-process limit
[REDACTED]		

(b) (4)

The formulation and process development were well carried out using QbD and risk assessment approaches. The applicant has gained extensive experience in manufacturing of the product for clinical use in both pilot scale (b) (4) and large scale ((b) (4)). Batch analysis data for all the batches manufactured showed that results of all tests were well within specifications and the impurity level was < (b) (4) There are no major quality concerns noted during the review process. However, the following items are suggested for considerations in the inspection:

Table 2

Concern	Item suggested for considerations
	(Delete as this would be part of basic inspection of quality system)
There are proposed design space boundaries for each unit operations	<ul style="list-style-type: none">• How are the design space boundaries captured in the master batch record and change control processes?

The ONDQA reviewers would be happy to meet with the OC and ORA representatives to discuss further, if desired. If possible, the reviewer would like to participate in a pre-approval inspection for the drug product manufacturing sites.

Thomas Wong (301-796-1608)
Quality Reviewers, DPA1

Ramesh Sood (301-796-1466)
ONDQA Branch Chief, DPA 1

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

THOMAS M WONG
03/05/2010

RAMESH K SOOD
03/09/2010

Office of New Drug Quality Assessment

DATE: February 22, 2010
TO: NDA 22-433 Extended Review Team
FROM: Chhagan Tele, Ph.D. (Drug Substance)
THROUGH: Christine Moore, Ph.D.
SUBJECT: Considerations for Inspection (CFI) of AstraZeneca for NDA 22-433

NDA 22-433 was submitted by AstraZeneca LP for Brilinta™ (ticagrelor) 90 mg immediate release film-coated tablets. The proposed indication is for reduction of rate of thrombotic events (including stent thrombosis) in patients with acute coronary syndromes who are to be managed medically or invasively with percutaneous coronary intervention and/or coronary artery bypass graft.

This memo includes an overview of the drug substance manufacturing process and findings from the CMC review. This NDA submission contained QbD information for the development of the drug substance. The applicant used combination of (b) (4) approach to define design space boundaries in each of the manufacturing unit operations. These findings are for consideration by the Office of Compliance and Office of Regulatory Affairs regarding pre-approval inspection.

Drug Substance

Ticagrelor is manufactured by a conventional (b) (4) scheme from (b) (4) designated starting materials. The drug substance, ticagrelor will be manufactured exclusively by AstraZeneca, Sodeltarje in Sweden or (b) (4) for commercial use. The commercial batch size of the drug substance to be manufactured is (b) (4). The applicant has employed some of the concepts and principles of Quality by Design (QbD) approach to the development of the ticagrelor (b) (4) route and manufacturing process. A risk assessment has been performed based on the current process understanding and prior knowledge. Failure Mode, Effects and Criticality Analysis (FMECA) was used for risk assessments throughout the development.

Flow Diagram of Manufacturing Process for Ticagrelor



(b) (4)

Design space boundaries, consisting of a multi-dimensional combination of parameters (e.g. mol. equivalents of reagents, time and temperature) have been defined which allow CQAs like impurities to be within target values. Similarly, design space boundaries for polymorphic form, particle size and the genotoxic impurity (b) (4) have been defined. The critical process parameters are amounts, reaction time, and reaction temperature in the process of (b) (4), and ticagrelor formation.

There are no major quality concerns noted during the review process. However, following findings are for consideration during pre-approval inspection:

- The proposed design space boundaries in each unit operations appeared to be appropriate and acceptable. However, inspector should verify these boundaries in the production/process qualification master batch record to be consistent with these boundaries, especially for the following items:

The ONDQA reviewer would be happy to meet with the OC and ORA representatives to discuss further, if desired. If possible, the reviewer would like to participate in a pre-approval inspection for the drug substance manufacturing site.

Chhagan Tele (301-796-1762)
ONDQA Quality Reviewer, DPA1

Ramesh Sood
Branch Chief, DPA 1
ONDQA/OPS/CDER/FDA
301-796-1466

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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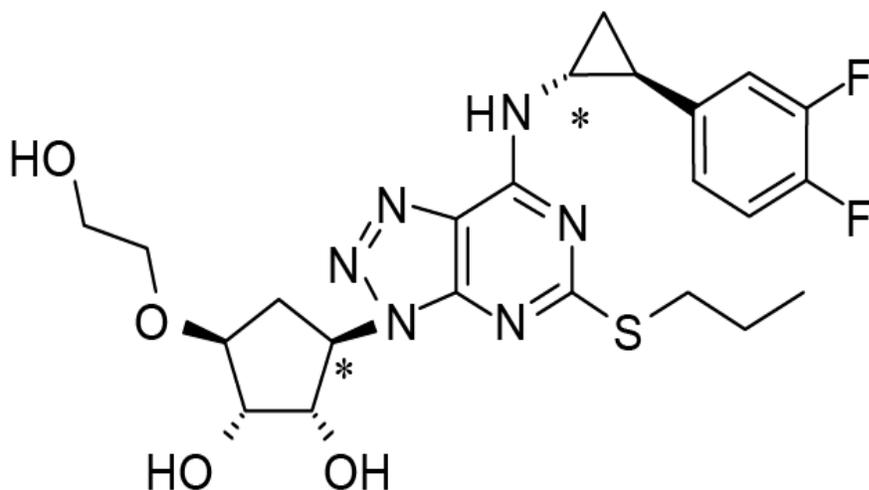
/s/

CHHAGAN G TELE
03/04/2010

RAMESH K SOOD
03/08/2010

Initial Quality Assessment Branch I

OND Division:	Division of Cardiovascular and Renal Products
NDA:	22-433
Applicant:	Astra Zeneca
Letter Date:	16 Nov 2009
Stamp Date:	16 Nov 2009
PDUFA Date:	16 May 2010
Tradename:	Brilinta
Established Name:	Ticagrelor
Dosage Form:	Tablets, 90 mg
Route of Administration:	Oral
Indication:	Reduction of rate of thrombotic events (including stent thrombosis) in patients with acute coronary syndromes who are to be managed medically or invasively with percutaneous coronary intervention and/or coronary artery bypass graft.
Assessed by:	Kasturi Srinivasachar
ONDQA Fileability:	Yes



Summary

This NDA is an eCTD submission for a new molecular entity, ticagrelor, a reversible inhibitor of platelet aggregation. This drug is the first of a new chemical class of antiplatelet agents called cyclopentyltriazolopyrimidines. Clinical development was carried out under IND 65,808 and the efficacy and safety of ticagrelor is derived mainly from a large Phase 3 study comparing this drug with clopidogrel. An End of Phase 2 CMC meeting was scheduled for Sep 19, 2007 but was cancelled as a result of the comprehensive Agency responses to questions in the briefing document. Agreement was reached on the designation of (b) (4)

(b) (4)
A Pre-NDA meeting was held with ONDQA staff on Jan 16, 2009 to discuss CMC aspects of the forthcoming NDA with particular emphasis on QbD elements proposed for inclusion. Astra Zeneca had proposed, (b) (4)

The Agency responded that this was not a design space as defined in ICH Q8 and that this sort of flexibility would be better addressed via a comparability protocol. Similar flexibility was sought for (b) (4)

Astra Zeneca were told that comparability protocols for such changes would be more appropriate. A definitive response to other changes proposed, e.g. (b) (4) for ticagrelor was not provided since it would depend on the evaluation of the supporting data provided in the NDA. The drug product discussions revolved around development of a discriminating dissolution method for this BCS Class 4 compound and a proposed design space for the (b) (4) step in the manufacturing process. The Agency responded to the planned control strategy to test ID, assay and dissolution (b) (4) by stating that adequate justification and supporting data would be needed in the NDA for this approach to be acceptable. Regarding Astra Zeneca's plan (b) (4)

Drug Substance

Ticagrelor is a (b) (4) crystalline powder with melting point 140°C - 142°C. It has (b) (4)

(b) (4)
It does not exhibit pH dependent solubility and belongs to BCS Class 4 (low solubility and low permeability). 4 (b) (4) polymorphs have been identified and (b) (4) has been selected for development. This form has been used in all pre-clinical and clinical studies and has been shown not to convert to any other form on storage. Ticagrelor is manufactured by a conventional (b) (4) scheme from (b) (4) designated starting materials. (b) (4)

Comprehensive studies have been carried out to understand the potential impurities and degradation products which may be present in ticagrelor. In addition, a comprehensive risk

based process has been used to ensure that the levels of potential genotoxic impurities present in the drug substance are below the Threshold of Toxicological Concern as defined in the EMEA guidance. Based on genotoxicity tests, the applicant concludes that only one impurity, (b) (4), needs to be controlled in the drug substance.

The drug substance specification is traditional and does not seek any real time release flexibility. It includes a test for polymorphic form using XRPD. Primary stability data up to 12 months are available for 3 batches manufactured at a scale that is representative of larger scale commercial production in a facility on the site where commercial manufacturing is proposed. In addition, 3 months' data for one batch manufactured at another proposed commercial manufacturing site have been provided as supporting data. A re-test period of (b) (4) is requested for ticagrelor stored at or below 30°C in the primary packaging.

QbD Aspects

Some of the concepts and principles of Quality by Design, as outlined in ICH Q8, have been applied to the development of the drug substance. CQAs have been identified and risk assessment processes have been used to define the experimental work performed. The Applicant claims to have gained a thorough understanding of the manufacturing process and the quality attributes of the drug substance and used this to define a design space. Control strategies have been proposed to ensure that routine operation of the manufacturing process remains within the design space so that CQAs are delivered consistently. Drug substance CQAs identified are:

- Description
- Identity
- Assay
- Absolute configuration
- Organic impurities
- Solvents
- (b) (4)
- (b) (4)
- Polymorphic form
- Particle size
- Metals
- Microbiology

Some of the CQAs showed low risk to be affected by process parameters whereas others were identified to potentially be controlled by process parameters. Not all CQAs are confirmed by end product testing in the ticagrelor specification.

Design space boundaries, consisting of a multi-dimensional combination of parameters (e.g. mol.equivalents of reagents, time and temperature) have been defined which allow CQAs like impurities to be within target values. Similarly, design space boundaries for polymorphic form, particle size and the genotoxic impurity (b) (4) have been defined. The knowledge gained during development is based mainly on the analysis of laboratory experiments. Scale-up experiments, modeling of scale dependent parameters and scientific rationale have been used to investigate potential scale up effects. It is claimed that these assessments establish that data generated at laboratory scale can be considered representative for commercial scale manufacture and that no changes in ticagrelor quality result from changes in equipment and scale from laboratory to pilot plant and commercial scale.

The control strategy for ticagrelor ensures that routine manufacture remains within the boundaries of the established design space and is based on the use of cGMP, specifications for starting materials and isolated intermediates, in-process controls, and drug substance specifications. A change management process is provided which includes an assessment whether the proposed change falls within, or is outside, the approved design space.

Drug Product

One strength of the product, 90 mg, has been developed as immediate release film coated tablets for commercialization. The tablet cores contain (b) (4)

(b) (4) hypromellose 2910, titanium dioxide, talc, polyethylene glycol 400 and ferric oxide yellow are also compendial. The formulation used in Phase 3 clinical trials is the same as that proposed for marketing with the exception of (b) (4). A conventional (b) (4) method has been used throughout development of ticagrelor tablets. (b) (4)

(b) (4) The product is packaged in HDPE bottles (b) (4) with (b) (4) child resistant closures and blister packs formed from (b) (4) sealed to (b) (4) aluminium foil.

The product specification is comprised of standard test attributes for solid oral dosage forms with the provision that all tests, excluding Description, (b) (4)

(b) (4) Stability testing has been carried out on 3 production scale batches of ticagrelor packaged in HDPE bottles, blister packs and bulk packs. The tablets were manufactured at the commercial manufacturing facility and are the same as the to-be-marketed tablets (b) (4). 12 months' data are currently available and a shelf life of 24 months is proposed for storage at 25°C. (b) (4)

QbD Aspects

The development of the ticagrelor tablets formulation and manufacturing process was directed using quality risk management (ICH Q9) and by applying the pharmaceutical development principles in ICH Q8. Failure Mode, Effects and Criticality Analysis (FMECA) was the main tool employed for risk assessment and each potential failure mode was assigned a Risk Priority Number (RPN). RPNs, in addition to criticality, were used to ensure that the highest magnitude risks were evaluated as a priority. Increased knowledge from experimental studies allowed a design space and control strategy to be defined for ticagrelor tablets to ensure consistent delivery of product CQAs. This systematic risk-based approach to the development of ticagrelor tablets starts with the definition of product quality attributes to be delivered with emphasis on CQAs, uses prior knowledge to identify risks and proceeds to formulation/process development using new knowledge based on in vivo studies and (b) (4) DOEs including clinically relevant in vitro tests to assess the effect of varying formulation and process. The knowledge gained is used to define a multidimensional design space, including both formulation and process boundaries,

that delivers product CQAs. Finally, a control strategy is described to ensure that routine operation remains within the design space.

The following CQAs were identified for the drug product during the course of development:

- Description
- Identification
- Assay
- Uniformity of Dosage Units
- Degradation Products
- Dissolution
- Microbiological quality

Since ticagrelor is a BCS class 4 compound, there is potentially a higher risk that changes in formulation and processing parameters can affect clinical performance. Initial risks were partially reduced by process type selection, formulation development and optimization studies.

(b) (4)

Excipient compatibility studies in combination with a knowledge of ticagrelor properties allowed a selection of excipients. The formulation was optimized using (b) (4) experimental designs. It is claimed that these studies led to a robust Phase 3/commercial formulation. After this formulation was established, a risk assessment was performed to identify formulation and process variables which might impact CQAs. In order to understand where controls might be required to ensure consistent in vivo performance, and to pinpoint areas where a broader design space could be defined, an in vivo volunteer study was carried out (clinical study 55). The aim of this study was to assess the pharmacokinetics of tablet variants manufactured to incorporate the highest risk formulation and process variables. In vitro dissolution characteristics of the tablet variants were also studied to establish a link between in vitro dissolution and in vivo pharmacokinetics through use of a relevant specification to assure in vivo performance. This study showed that the highest risk formulation and process variables had no impact on the in vivo pharmacokinetics within the ranges investigated. The Applicant concludes that the commercial formulation is insensitive to these high risk changes and hence allows for a flexible design space. It is claimed that this study also enabled the establishment of a clinically relevant dissolution specification.

The ticagrelor tablet design space is specified in terms of (b) (4)

The control strategy for ticagrelor tablets is designed to ensure that routine drug product manufacture remains within the design space so that CQAs are consistently delivered. It includes control of input materials, controls for unit operations, in- process controls and end-product testing. It is stated that part of the ticagrelor tablets control strategy allows for reduced end-product testing due to increased knowledge and understanding and the application of in-process controls. This reduction, which applies to routine operation within the design space, involves:

- (b) (4)
- (b) (4)

The Applicant states that the design space and control strategy will be operated within the framework of their Quality System which includes change management. Changes will be evaluated and implemented in accordance with cGMP and ICH guidelines. If the proposed change falls within the design space no regulatory notification will be given prior to implementation. However, if the proposed change falls outside of the registered design space, regulatory approval will be sought before implementation.

Critical Issues for Review

Drug Substance

- Have adequate data been submitted in support of the strategy for (b) (4)
- At a pre-NDA meeting, the Applicant had proposed (b) (4)
They were told that this was not acceptable and that they could instead submit comparability protocols to achieve some degree of flexibility. A quick perusal of the submission did not reveal such protocols but the reviewer should confirm that this option has not been pursued.
- The Applicant had also proposed to include, as part of the design space, any unit operation, type of equipment or technology to (b) (4)
Have they provided data in support of this proposal including an evaluation of downstream risks, impurity profile comparisons etc.?
- Similarly, have they provided adequate data in support of their proposal for any change in scale or equipment made in accordance with the outcome of the risk assessment?
- Section 3.2.S.6 should be critically evaluated since this Manufacturing Process Development section contains the QbD aspects of the drug substance. (b) (4)
- (b) (4) have hold times for these been specified and supported with data?
- Do (b) (4) manufacturing facilities listed, Astra Zeneca and (b) (4) perform only the step from the (b) (4) to the final drug substance?
- Should an identification test be included in the specifications of the (b) (4)
- Are the proposed impurity limits in the specification for (b) (4) adequately justified? Since none of these is listed in the drug substance specification, are they effectively (b) (4) ?
- Are the specified impurities with limits above (b) (4) in the drug substance specification properly qualified in the pre-clinical studies? Pharmacology/toxicology input may be needed.
- Regarding the screening program for genotoxic impurities, have the concerns raised at the pre-NDA meeting on April 20, 2009 been addressed?

- Genotoxicity tests were performed on 5 impurities and based on the results only one impurity (b) (4) was selected for inclusion in the drug substance specification. The adequacy of this should be evaluated in consultation with the pharmacology/toxicology reviewer.
- Polymorphic (b) (4) was chosen for development even though this form is (b) (4). Has the Applicant convincingly demonstrated that operating within the design space and adherence to the prescribed control strategy will consistently yield only (b) (4) ticagrelor with no contamination from other forms? Is there any possibility of form conversion during drug substance storage, drug product manufacture or drug product storage?
- Is the XRPD method, used to confirm the presence of (b) (4) in the drug substance specification, capable of quantifying other forms, like (b) (4), that could potentially be present?
- Has the Applicant adequately justified the proposed particle size distribution acceptance criteria in the specification?
- Is the limit of NMT (b) (4) for (b) (4) justified? Is it acceptable to omit testing for (b) (4) from the specification?
- Has adequate risk assessment been carried out to justify the omission of the routine (b) (4) (b) (4) from the specification?
- Should a specific optical rotation test be included in the specification?

Drug product

- The development of the dissolution method and acceptance criteria, including the late change in (b) (4) (b) (4) should be evaluated by the Biopharmaceutics reviewer from ONDQA assigned to this NDA. Since the P.2 Pharmaceutical development section includes dissolution data to support key conclusions from the development studies, and in development of the design space, it should be reviewed by both Biopharmaceutics and CMC reviewers. The in vivo evaluation of various formulation and process variants (clinical study 55) and investigation of the relationship between in vitro dissolution and in vivo performance is also the responsibility of the Biopharmaceutics reviewer.
- Has the Applicant substantiated the claim that (b) (4)
- Have the excipient compatibility studies been properly executed and documented?
- The Pharmaceutical Development section 3.2.P.2 should be reviewed in detail with particular attention to the derivation of the design space boundaries for each unit operation. (b) (4)
- (b) (4)
- Has the applicant provided suitable justification for (b) (4)
- Is the rationale provided for not testing (b) (4) acceptable?
- A NIR method has been proposed for assay and identification of ticagrelor in the drug product specification. Has the method been properly validated to establish its suitability

for this purpose? Since the specification sheet lists 3 procedures (NIR or HPLC or UPLC), it should be clarified which is the regulatory method and which are alternative methods.

- Since uniformity of dosage units testing at release is by weight variation, as allowed by USP, are there any in-process tests for [REDACTED] (b) (4) [REDACTED] Are such tests needed for added assurance?
- The applicant is proposing a [REDACTED] (u) (4) [REDACTED] expiration dating period for all packaging configurations based on 12 months' long term data. Do they meet the conditions laid out in ICH Q1E for this extrapolation?

Comments and Recommendations

The application is fileable. Facilities have been entered into EES and the reviewers should verify the accuracy of the entries. This NDA contains elements of QbD in both drug substance and drug product sections and it is recommended that reviewers with the appropriate background be assigned. A full environmental assessment report has been submitted and a consult request to OPS EA staff will be sent.

Kasturi Srinivasachar, Ph.D.
Pharmaceutical Assessment Lead
Ramesh Sood, Ph.D.
Branch Chief

Dec. 11, 2009
Date
Dec. 11, 2009
Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22433	ORIG-1	ASTRAZENECA LP	AZD6140

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/s/

KASTURI SRINIVASACHAR
12/11/2009

RAMESH K SOOD
12/11/2009