

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022433Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 022433

SUPPL #

HFD # 110

Trade Name Brilinta

Generic Name ticagrelor

Applicant Name AstraZeneca

Approval Date, If Known July 20, 2011

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

- b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

Investigation #2

!

YES

! NO

Explain:

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Michael Monteleone
Title: Regulatory Health Project Manager
Date: July 18, 2011

Name of Office/Division Director signing form: Norman Stockbridge, MD, PhD
Title: Director, Division of Cardiovascular and Renal Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

MICHAEL V MONTELEONE
07/20/2011

NORMAN L STOCKBRIDGE
07/20/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

WHITE OAK COMPLEX
10903 NEW HAMPSHIRE AVE
BLDG. 22
SILVER SPRING, MD 20993



US Mail address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardiovascular and Renal Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 1.302.885.4048

Subject: Meeting Minutes

Date: May 19, 2011

Pages including this sheet: 5

From: Mike Monteleone

Phone: 301.796.1952

Fax: 301.796.9841

Meeting Minutes

Application: NDA 022433
Sponsor: AstraZeneca
Drug: Brilinta (ticagrelor)
Type of Meeting: Advice

Date of Meeting: April 20, 2011

List of FDA Meeting Participants:

** Office of Drug Evaluation I*

Robert Temple, MD	Director
Ellis Unger, MD	Deputy Director

** Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Stephen M. Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Thomas Marciniak, MD	Clinical Team Leader
Melanie Blank, MD	Clinical Reviewer
Martin Rose, MD	Clinical Reviewer
Thomas Papoian, PhD	Pharmacology Team Leader
Elizabeth Hausner, DVM	Pharmacologist
Michael Monteleone, MS	Regulatory Project Manager

**Office of Biostatistics, Division of Biometrics I*

Jim Hung, PhD	Director
Jialu Zhang, PhD	Biostatistician

**Office of Clinical Pharmacology, Division of Clinical Pharmacology I*

Sudharshan Hariharan, PhD	Clinical Pharmacologist
Islam Younis, PhD	Clinical Pharmacologist

**Office of Surveillance and Epidemiology, Division of Risk Management*

Cynthia LaCivita, PharmD	Drug Risk Management Analyst
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List of Sponsor Meeting Participants:

Kevin J. Carroll, MSc	Vice President Statistics, Chief Statistician
Simon Clowes, BSc (Hons)	Global Product Vice President
Jonathan C. Fox, MD, PhD	Vice President, Clinical Therapeutic Area, Cardiovascular and Gastrointestinal Diseases
Alex Gold, MD	Executive Director, Clinical Development
Peter Honig, MD	Vice President, Global Regulatory Affairs
Barry Sickels	Vice President, AZ Regulatory Affairs
Mary Whealy	Global Regulatory Affairs Director
Sven Nylander, PhD	Discovery Project Leader
Hans van Giezen, PhD	Innovative Medicines Project Director

Background:

The sponsor submitted an original NDA for Brilinta (ticagrelor) for treatment of ACS on November 16, 2009. The application was designated for standard review with a PDUFA goal date of September 16, 2010, which later was adjusted to December 16, 2010 because of submission of a major amendment. An Advisory Committee meeting was held on July 28, 2010. The Agency issued a Complete Response letter on December 16, 2010. The sponsor resubmitted their NDA on January 20, 2011 and the Agency acknowledged, in a letter dated February 3, 2011, that it was a complete, Class 2 resubmission with a July 20, 2011 PDUFA goal date. The sponsor requested a meeting with the Agency at the review cycle mid-point to discuss the progress of the review. That meeting took place on April 20, 2011. The minutes of that meeting follow.

Minutes:

After introductions, Dr. Temple opened the meeting by advising the applicant that primary reviews are not complete and so the Agency's review is still ongoing. Dr. Temple said that until a decision is made about the importance of the apparent interaction between dose of aspirin and ticagrelor, drafting labeling is problematic, though it should proceed quickly once a decision is reached.

The applicant's proposed REMS was briefly discussed. Dr. LaCivita commented that the proposed REMS was generally in line with Agency expectations. However, it is likely that some changes will be necessary with the changes being dependent on the completed label. She thought these changes would be relatively easy to implement. Dr. LaCivita advised that she may have specific comments for the sponsor once she completes her interim review.

Dr. Temple commented on the applicant's response to the Agency's Complete Response letter, stating that though the Agency's review is still ongoing, the finding of an interaction between dose of aspirin and ticagrelor appears robust to multiple methods of imputing aspirin dose and analyses of the interaction. Dr. Temple cautioned that he was mindful of the Advisory Committee's conclusion that the aspirin interaction was a chance finding. Dr. Temple stated that no one has been persuaded that a biologically plausible mechanism for an interaction between aspirin dose and ticagrelor has been identified.

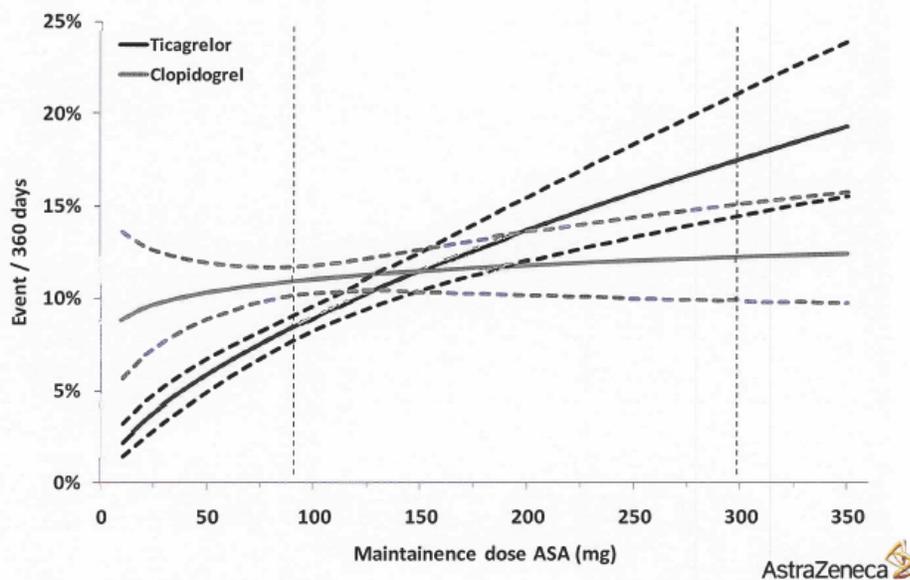
The biologic plausibility of the aspirin hypothesis was briefly discussed. Dr. Hausner advised that she had everything she needed from the applicant to complete her review. Dr. Papoian noted that the *in vitro* platelet data showed that although aspirin enhanced the anti-platelet effect when P2Y12 inhibition was partial, no additional platelet inhibition was observed when aspirin was increased from 30 uM to 120 uM, indicating that even concentrations of aspirin (30 uM) equivalent to exposure following a low dose (75 mg) in humans were already producing a maximal effect. Therefore, the sponsor's hypothesis that aspirin enhanced clopidogrel's partial P2Y12 blockade, but not ticagrelor's complete blockade, was not supported, at least by the *in vitro* data. The applicant appeared to agree with that interpretation.

The applicant mentioned the recent publication of a focused ACC/AHA Guideline that advises use of a low maintenance dose of aspirin (75-162 mg) for primary prevention. Dr. Blank asked the applicant to submit the reference and any other relevant information.

There was some discussion regarding an applicant handout, Figure 1, below. Dr. Temple commented that the graph showed that high dose aspirin has no effect on clopidogrel. The Division inquired why the confidence interval around the point estimate for event rates in subjects on ticagrelor at varying doses of aspirin does not splay out at lower doses of aspirin, as the one for clopidogrel does. The applicant commented that the splaying is a result of smaller numbers of patients on the different extremes of aspirin dose and resultant larger confidence intervals. The applicant commented that if ticagrelor were carried back to a zero dose of aspirin it would also splay. Dr. Papoian made the comment that the applicant's figure indicated that the lowest event rates were observed in ticagrelor subjects not administered any aspirin.

FIGURE 1

Event rates differ at lower ASA doses; at higher doses event rate CIs overlap.



There was some discussion regarding the applicant's internal procedures for handling of adverse event reporting. Dr. Marciniak asked why the applicant had not expedited the reporting of serious and unexpected adverse events in two PLATO subjects, one an out-of-hospital arrest with seizure in a patient with subsequent in-hospital AV block and the other a subject hospitalized with headache and an unspecified abnormality on cerebral scans. For both patients the investigator discontinued study drug because of the serious adverse event (SAE). The applicant replied that the investigator had indicated that the SAEs were unrelated to study drug and that it was company policy to accept investigator determination of relatedness. Dr. Marciniak noted that under FDA's new reporting rule it is the applicant's responsibility to determine relatedness of serious unexpected adverse events, although that was not clear at the time of reporting. Dr. Rose raised a question regarding a recent initial reporting of an AV block SAE. He asked why the name and address of the reporter were marked as private. The applicant commented that under German law they are limited in the information they can gather. Dr. Marciniak asked why the listing of prior AV block AEs included with the SAE report for this patient (see Figure 2) listed no prior AV block adverse events (AEs). The applicant responded that the listing only included AEs submitted post-marketing.

FIGURE 2

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2011SE19562

Date: 14-APR-2011

LISTING OF PRIOR SAFETY REPORTS
SUBMITTED TO IND # 65,808

ADVERSE EVENT: Atrioventricular block
(all preferred and included coded terms)

Manufacturer Report # FDA Submission Date Protocol Number
No safety reports have been previously submitted to the IND for this adverse event.

Country of Origin

Signature, Meeting Chair: *{See appended electronic signature page}*
Robert Temple, MD

Reviewed:

MMonteleone	21 APR 11 (Drafted)
CLaCivita	21 APR 11
TMarciniak	28 APR 11
MBlank	28 APR 11
MRose	28 APR 11
EHausner	28 APR 11
TPapoian	28 APR 11
JZhang	29 APR 11
SGrant	09 MAY 11
NStockbridge	09 MAY 11
EUnger	11 MAY 11
RTemple	16 MAY 11

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/s/

ROBERT TEMPLE
05/19/2011



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We are reviewing the carton and container labeling of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. General Comments (All labels and Labeling)

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e., Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the established name shall be printed in letters that are at least half as large and a prominence commensurate with the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.

B. Container Labels-180 count

1. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.
2. Minimize the size of the company name and logo.

C. Container Labels-60 count

1. See comment B.1. and B.2. above.

2. The principal display panel is crowded. To minimize overcrowding condense the manufacturer's address statement.

D. Professional Samples-8 count

The principal display panel of the container label is crowded. To minimize overcrowding, relocate the statement, "Each tablet contains 90 mg ticagrelor" to the top of the left side panel. In order to accommodate this, minimize or remove the statement "Brilinta is a trademark...AstraZeneca 2010".

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

NORMAN L STOCKBRIDGE
05/13/2011



NDA 022433

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca LP
1800 Concord Pike
P.O. BOX 8355
Wilmington, DE 19803-8355

ATTENTION: Emery Gigger
Director, Regulatory Affairs

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor Tablets, 90 mg.

We also refer to your January 24, 2011, correspondence, received January 24, 2011, requesting review of your proposed proprietary name, Brilinta. We have completed our review of the proposed proprietary name, Brilinta, and have concluded that it is acceptable.

The proposed proprietary name, Brilinta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your January 24, 2011 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone at 301-796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
04/15/2011

**DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS
FOOD AND DRUG ADMINISTRATION**

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FDA/CDER/DCaRP 5901-B Ammendale Rd. Beltsville, MD 20705-1266

Transmitted via Email: Emery.Gigger@astrazeneca.com

Attention: Emery Gigger

Company Name: AstraZeneca

Phone: 1.302.885.4048

Subject: Meeting Minutes

Date: February 16, 2011

Pages including this sheet: 4

From: Mike Monteleone
Phone: 301.796.1952
Fax: 301.796.9841

Meeting Minutes

Application: NDA 022433
Sponsor: AstraZeneca
Drug: Brilinta (ticagrelor)
Type of Meeting: Advice

Date of Meeting: February 4, 2011

List of FDA Meeting Participants:

** Office of Drug Evaluation I*

Robert Temple, MD	Director
Ellis Unger, MD	Deputy Director

** Division of Cardiovascular and Renal Products*

Norman Stockbridge, MD, PhD	Director
Stephen M. Grant, MD	Deputy Director
Mary Ross Southworth, PharmD	Deputy Director for Safety
Tom Marciniak, MD	Clinical Team Leader
Melanie Blank, MD	Clinical Reviewer
Elizabeth Hausner, DVM	Pharmacologist
Ed Fromm, RPh, RAC	Chief Project Manager
Michael Monteleone, MS	Regulatory Project Manager

**Office of Biostatistics, Division of Biometrics I*

Jim Hung, PhD	Director
Jialu Zhang, PhD	Biostatistician
John Lawrence, PhD	Biostatistician

**Office of Surveillance and Epidemiology, Division of Risk Management*

LCDR Latoria Ford	Patient Labeling Reviewer
Cynthia LaCivita	REMS Reviewer

List of Sponsor Meeting Participants:

Peter Honig, MD	Vice President, Global Regulatory Affairs
Jonathan C. Fox, MD	Vice President, Clinical Therapeutic Area, Cardiovascular and Gastrointestinal Diseases
Kevin J. Carroll, MSc	Vice President Statistics, Chief Statistician
Simon Clowes, BSc (Hons)	Global Product Vice President
Alex Gold, MD	Executive Director, Clinical Development

Background:

The applicant submitted an original NDA to market Brilinta (ticagrelor) for treatment of ACS on 16 November 2009. An Advisory Committee (AC) meeting was held to discuss aspects of the application on 28 July 2010. The Agency issued a Complete Response letter to the applicant on 16 December 2010. The applicant resubmitted their NDA on 20 January 2011. In a letter dated 03 February 2011, the Agency acknowledged the resubmission was a complete, Class 2 resubmission with a 20 July 2011 PDUFA goal date. In response to a request from the applicant, a meeting was held to discuss their resubmission on 04 February 2011.

Minutes:

The applicant began the meeting by thanking the Agency for its time and confirming receipt of the Agency's Acknowledgment letter the day before. The sponsor also indicated that they realized that the decision on their

NDA would be difficult and expressed a desire to work with the Agency to conduct an efficient and expeditious review.

The applicant presented a number of slides giving an overview of their Resubmission [see attached]. They commented that they believe the submitted analyses confirm their conclusion in the original submission that the regional interaction observed in North America is explained by an interaction of ticagrelor with aspirin (ASA).

There was some discussion around slide 7, describing a particular PLATO subject's ASA records; Dr. Marciniak commented that patients without aspirin records probably did not receive aspirin and should be assigned a dose of zero. The applicant responded that they analyzed all patients using a number of possible imputation methods as requested in the Agency's Complete Response letter, including assigning zero dose for patients without ASA records.

There was some discussion around how and when aspirin dosage was recorded.

There was also discussion exploring stenting and other factors that may have influenced the ASA dose that subjects received (so that such a factor might explain the outcome effect being attributed to aspirin). The applicant said that they had looked at numerous factors and were not able to find one that influenced ASA dosage. Dr. Marciniak commented that he thought there were factors that influenced ASA dosage and he is also looking at what other factors correlate with outcomes. He noted that for all cause mortality there are interactions between ticagrelor use and CYP3A4 statin use and stenting and none with ASA dosage. He agreed to provide his analyses to the applicant.

Dr. Temple asked the applicant to comment on slide 16 of their presentation because this was the one analysis that did not show a strong aspirin dose interaction. The sponsor commented that this analysis includes the first day ASA dose.

Dr. Temple noted that most of the AC members believed that the discrepancy in US/OUS outcomes was a chance finding. The applicant responded that chance can never be eliminated as a possibility but given the current evidence, ASA seems to be the most likely explanation. There was discussion of the fact that ASA dose is a post-randomization characteristic and that it could be a consequence of some subject characteristics that themselves correlated with outcomes. If that were the case it could be the characteristic, not ASA, creating the disparate results. For this to be so, however, it was pointed out, the characteristic that led to high aspirin dose would need to have its effect only on the ticagrelor patients.

Dr. Grant asked the applicant to comment on whether they had additional data that would provide a biologic explanation for the ASA interaction. The applicant responded that they are not much further along in their understanding of the interaction than they were at the AC. There is no direct evidence of a harmful effect on the endothelium from the interaction between high dose aspirin and ticagrelor but they have done some animal work that they have submitted to the NDA that they want us to consider. The applicant commented that given the dearth of data showing any benefit of high dose over low dose ASA they did not see a need to define a population that may require high dose ASA in conjunction with ticagrelor.

The sponsor asked if an additional clinical trial will be required before approval. Dr. Temple commented that although the AC and the applicant's advisor wanted another confirmatory clinical trial, perhaps after approval, the Agency has not determined whether an additional trial is necessary. Dr. Temple reiterated that, as described in the Agency's Complete Response letter, before an Approval decision can be contemplated the Agency must have a thorough understanding of the ASA interaction in the trial. Dr. Temple also advised that there are still a number of analyses underway and that the Division would provide feedback on those following the meeting.

Signature, Meeting Chair: *{See appended electronic signature page}*
Robert Temple, MD

Reviewed:

MMonteleone	07 FEB 11 (drafted)
EFromm	07 FEB 11
JZhang	09 FEB 11
JHung	09 FEB 11
MBlank	09 FEB 11
TMarciniak	10 FEB 11
SGrant	10 FEB 11
NStockbridge	11 FEB 11
RTemple	15 FEB 11
MMonteleone	16 FEB 11 (finalized)

Attachment:

Applicant's Slides

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/s/

ROBERT TEMPLE
02/16/2011



NDA 022433

**ACKNOWLEDGE –
CLASS 2 RESPONSE**

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

We acknowledge receipt on January 20, 2011, of your January 20, 2011, resubmission of your new drug application submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brilinta (ticagrelor) 90 mg tablets.

We acknowledge your request that this resubmission be considered a class 1 resubmission, but because of the critical and extensive nature of the submitted analysis, as well as your submission of a proposed REMS containing a communication plan we consider this a complete, class 2 resubmission to our December 16, 2010, action letter. Therefore, the user fee goal date is July 20, 2011.

If you have any questions, call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

EDWARD J FROMM
02/03/2011

Monteleone, Michael V.

Subject: RE: Call from AZ

From: Jenkins, John K
Sent: Tuesday, December 14, 2010 3:32 PM
To: Temple, Robert; Stockbridge, Norman L; Unger, Ellis; Woodcock, Janet
Cc: Kweder, Sandra L; Jenkins, John K
Subject: Call from AZ

Bob and others

I [REDACTED] (b) (5)

[REDACTED]

[REDACTED]

[REDACTED]

John

John K. Jenkins, M.D.
Director, Office of New Drugs
10903 New Hampshire Avenue
Bldg #22, Room 6304
Silver Spring, MD 20993
301-796-0700
301-796-9856 (fax)
NOTE, New E-mail Address: john.jenkins@fda.hhs.gov

Reference ID: 2877809

12/14/2010

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/s/

MICHAEL V MONTELEONE
12/14/2010



PDUFA GOAL DATE EXTENSION

NDA 022433

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your new drug application (NDA) originally submitted on November 13, 2009 and received November 16, 2009 under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Brilinta (ticagrelor) 90 mg tablets.

On June 21, 2010, we received your June 21, 2010, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 16, 2010.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely yours,

{See appended electronic signature page}

Edward Fromm, RPh, RAC
Chief, Project Management Staff
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

EDWARD J FROMM
09/14/2010



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the carton and container labeling of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

A. General Comments (All labels and Labeling)

1. We note the proprietary name is presented in all-caps. Consider revising the proprietary name to appear in title case (i.e. Brilinta). Words set in upper and lower case form recognizable shapes, making them easier to read than the rectangular shape that is formed by words set in all-caps.
2. Ensure the presentation of the established name is at least half the size of the proprietary name in accordance to 21 CFR 201.10(g)(2), which requires that the establish name shall be printed in letters that are at least half as large and with a prominence commensurate to the proprietary name, taking into consideration all pertinent factors, including typography, layout, contrast and other printing features.
3. Increase the prominence of the strength. The current presentation is difficult to read.

B. Container Labels-180 count

1. Relocate the statement "Dispense with Medication Guide" to the Principal Display Panel (PDP) to ensure the statement is not overlooked by health care practitioners. To accommodate this modification and prevent over-crowding of the PDP, relocate the statement, "Each tablet contains 90 mg ticagrelor" to the side panel of the container label.

2. We note that although the 180 count bottle may be a unit-of-use container, it may also be used for more than one patient. Ensure a sufficient number of medication guides are provided.

C. Container Labels-60 count

See comment B.1. above

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

NORMAN L STOCKBRIDGE
08/13/2010



NDA 022433

ADVICE

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the pharmacology section of your submission and have the following comments.

The Division met with the Executive Carcinogenicity Assessment Committee to discuss Astra Zeneca's proposed prolactin mechanism of carcinogenesis. Information provided to the Executive CAC included the material provided by Astra Zeneca (SDN 042, submitted July 16, 2010), the incidence tables for pituitary and mammary tumors and the minutes of the Executive CAC meeting where the rodent carcinogenicity studies were originally reviewed.

The Committee felt that since the proposed hypothesis is predicated upon a change in hormonal levels, it would be reasonable to demonstrate that change by measuring prolactin levels. However, even if decreased prolactin levels are found, those decreased levels are not necessarily linked to increased uterine tumors. Circulating hormone levels measured only in animals do not necessarily support that the uterine tumors will not occur in humans. As presented, the Executive CAC felt that there were insufficient data to support the hypothesis and insufficient evidence to discount the possible relevance of the observed carcinogenic effect to humans.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

NORMAN L STOCKBRIDGE
08/12/2010

Minutes of Division Discussion with Executive CAC for Ticagrelor

Executive CAC

Date of Meeting: August 3, 2010

Committee: David Jacobson-Kram, Ph.D. OND-IO, Chair
Abby Jacobs, Ph.D., OND-IO, Member
Paul Brown, Ph.D., OND-IO, Member
Haleh Saber, Ph.D., DHP, Alternate Member
Muriel Saulnier, D.V.M., Ph.D., Acting Supervisor
Elizabeth Hausner D.V.M, Reviewer

Coordinator: Adele Seifried, M.S. OND-IO

Author of minutes: E. Hausner, D.V.M.

NDA:22-433

Drug Name: ticagrelor (Brilinta™)

Sponsor: AstraZeneca

The Division met with the Executive CAC to request the committee's opinion on the sponsor's proposed hypothesis that the uterine tumors (a decreased prolactin mechanism proposed) and hepatic tumors (hepatic adaptation proposed) seen in the rat two year study were due to mechanisms that made the tumors irrelevant to humans.

The Committee felt that if a change in prolactin levels are cited as the mechanism, a change in the hormone level should at least be demonstrated. However, even if decreased prolactin levels are found, those decreased levels are not necessarily linked to increased uterine tumors. Circulating levels of prolactin measured only in animals also does not provide support that the uterine tumors will not occur in humans.

The consensus opinion of the Exec CAC was that there was insufficient evidence to support the hypotheses and insufficient evidence to discount the possible relevance of the observed carcinogenic effect to humans.

The Division requested that the Exec CAC address the following three questions:

1. Does the Executive CAC agree with the sponsor's proposed prolactin hypothesis?

Exec CAC answer: No.

2. Does the Executive CAC agree that the hepatic tumors are irrelevant to humans?

Exec CAC answer: It is not certain, although usually hepatic tumors in rodents are not considered relevant to humans..

3. 3. Does the Exec CAC agree that ticagrelor has no carcinogenic potential for humans?

Exec CAC answer: No.

David Jacobson-Kram, Ph.D.
Chair, Executive CAC

cc:\n
/Division File, DCRP
/M Saulnier, DCRP
/L Hausner, DCRP
/M Monteleone, DCRP
/ASeifried, OND IO

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

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/s/

ADELE S SEIFRIED
08/10/2010

DAVID JACOBSON KRAM
08/10/2010



NDA 022433

INFORMATION REQUEST

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your November 13, 2009 submission, containing a New Drug Application for Brilinta (ticagrelor).

We are reviewing the pharmacology section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

There are insufficient data to support the qualification of the impurity (b) (4) at a level of (b) (4) as requested in the NDA. Based on our concern that this impurity may possess genotoxic potential, it is recommended, as outlined in the ICH Guidance Q3A Impurities in New Drug Substances (Feb 2003), that a Bacterial Reverse Mutation (Ames) Test and a mammalian chromosomal aberration test be conducted with ticagrelor containing the impurity (b) (4) at a level (b) (4)

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796.1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

NORMAN L STOCKBRIDGE
07/12/2010

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Office/Division): PMHS		FROM (Name, Office/Division, and Phone Number of Requestor): Michael Monteleone, Division of Cardiorenal, x61952		
DATE 7-9-10	IND NO.	NDA NO. 22433	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 7-9-10
NAME OF DRUG Brilinta (ticagrelor)	PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG NME	DESIRED COMPLETION DATE August 10, 2010	
NAME OF FIRM: AstraZeneca				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL	<input type="checkbox"/> PRE-NDA MEETING	<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER		
<input type="checkbox"/> PROGRESS REPORT	<input type="checkbox"/> END-OF-PHASE 2a MEETING	<input type="checkbox"/> FINAL PRINTED LABELING		
<input type="checkbox"/> NEW CORRESPONDENCE	<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input checked="" type="checkbox"/> LABELING REVISION		
<input type="checkbox"/> DRUG ADVERTISING	<input type="checkbox"/> RESUBMISSION	<input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE		
<input type="checkbox"/> ADVERSE REACTION REPORT	<input type="checkbox"/> SAFETY / EFFICACY	<input type="checkbox"/> FORMULATIVE REVIEW		
<input type="checkbox"/> MANUFACTURING CHANGE / ADDITION	<input type="checkbox"/> PAPER NDA	<input type="checkbox"/> OTHER (SPECIFY BELOW):		
<input type="checkbox"/> MEETING PLANNED BY	<input type="checkbox"/> CONTROL SUPPLEMENT			
II. BIOMETRICS				
<input type="checkbox"/> PRIORITY P NDA REVIEW	<input type="checkbox"/> CHEMISTRY REVIEW			
<input type="checkbox"/> END-OF-PHASE 2 MEETING	<input type="checkbox"/> PHARMACOLOGY			
<input type="checkbox"/> CONTROLLED STUDIES	<input type="checkbox"/> BIOPHARMACEUTICS			
<input type="checkbox"/> PROTOCOL REVIEW	<input type="checkbox"/> OTHER (SPECIFY BELOW):			
<input type="checkbox"/> OTHER (SPECIFY BELOW):				
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION	<input type="checkbox"/> DEFICIENCY LETTER RESPONSE			
<input type="checkbox"/> BIOAVAILABILITY STUDIES	<input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS			
<input type="checkbox"/> PHASE 4 STUDIES	<input type="checkbox"/> IN-VIVO WAIVER REQUEST			
IV. DRUG SAFETY				
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL	<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY			
<input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES	<input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE			
<input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)	<input type="checkbox"/> POISON RISK ANALYSIS			
<input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP				
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL	<input type="checkbox"/> NONCLINICAL			
COMMENTS / SPECIAL INSTRUCTIONS: Please review the PI for new NDA 022433 Brilinta (ticagrelor), the pharmtox review is in DARRTS and labeling has been commented on by the tox reviewer, Dr. Elizabeth Hausner. I will send a word version of the commented upon labeling to Tammy Brent Howard via email.				
SIGNATURE OF REQUESTOR Mike Monteleone		METHOD OF DELIVERY (Check one) <input type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER		PRINTED NAME AND SIGNATURE OF DELIVERER		

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

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/s/

MICHAEL V MONTELEONE
07/09/2010



NDA 22-433

INFORMATION REQUEST

AstraZeneca
Attention: Emery Gigger, Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Gigger:

Please refer to your November 13, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor tablets.

We reviewed your Chemistry, Manufacturing, and Controls information and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Drug Substance:

1. Final (b) (4) are manufactured at several locations in (b) (4) and then presumably shipped to AstraZeneca, Sweden or (b) (4). Include an identification test in the acceptance criteria for these (b) (4).
2. (b) (4)
3. In 3.2.S.3.1, you stated that it was not possible to (b) (4) whereas the stereochemistry discussed in 3.2.S.3.2 was apparently based on exactly this technique. Clarify on this apparent inconsistency.
4. Include acceptance criteria for the (b) (4) in the drug substance specification.
5. Include method numbers in the drug substance specification table for the test methods used for the release and stability of the drug substance.
6. Provide the quantitation limit (QL) of the HPLC method for (b) (4) impurity.
7. Regarding polymorphic form:
 - a. The XRPD method is used to confirm the presence of Polymorphic (b) (4) in the drug substance specification. Provide data to support the capability of the XRPD method for the quantification of other polymorphic forms (b) (4) which could potentially be present.
 - b. Provide the experimental data used to justify the design space for ticagrelor crystallization. Include all relevant process inputs (e.g., concentrations, temperature, initial purity, scale, process time), the measured responses (e.g., purity, polymorphic percent), and any statistical analysis.

- c. [REDACTED] (b) (4)
Provide data, if available.
- d. It is noted in Section 7.5.1 in S.2.6 that a [REDACTED] (b) (4)
[REDACTED]
- e. Provide information about solubility of polymorph [REDACTED] (b) (4)
8. Provide stability commitment to include commercial batches manufactured at [REDACTED] (b) (4) site and Sodertalje, Sweden site.

Drug Product:

9. Provide the following data to support your proposed design space:

[REDACTED] (b) (4)

- c. The method that you used to determine the absence of Polymorph [REDACTED] (b) (4) during the tablet manufacturing process and the sensitivity of the method.
- d. Batch analysis data on validation batch(es) manufactured with the proposed commercial batch size and equipment when results are available.
10. Modify your process description in Section P.3.3 as follows:

[REDACTED] (b) (4)

11. Upon evaluation of the data provided, the Agency is in concurrence [REDACTED] (b) (4)
[REDACTED]
This test should be listed below the specification table (not within the table) and clearly labeled. Provide a testing frequency for this test and supporting rationale for the suggested frequency.

12. We acknowledge that the proposed in vitro dissolution acceptance criteria are based on demonstrated in vivo performance. However, the acceptance criteria for dissolution are generally set at Q [REDACTED] (b) (4) for an immediate release product; this criteria ensures that most of

the drug product will dissolve. The Agency recommends that the proposed dissolution specification be revised from (b) (4). Furthermore, Q (b) (4) is consistent with the provided data for the 41 clinical batches and the 10 commercial batches, showing that the dissolution values at 45 minutes (b) (4) within a reasonable range of variability. This revision will reduce the probability of releasing lots that are bioequivalent due to incomplete release of drug.

13. In order to support your proposal (b) (4)

14. In the footnote "a" of the drug product specification (b) (4)

15. Specify which are the primary and alternative analytical methods used for testing of identification, assay and degradation products of the drug product.

16. For NIR method validation:

18. Provide the specifications of the container closure systems in a tabular format. The information should include the description of the bottles (e.g. sizes and wall thickness, description of the closure, description of the blisters and the thickness of the (b) (4) the aluminum lidding foil, and the (b) (4)

19. Confirm that your design space for drug substance and drug product does not include a change in manufacturing site, to one not listed in the application. Note that at this time the agency does not have any mechanism to allow for site changes supported by a firm's Change Management Protocol.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22433

ORIG-1

ASTRAZENECA LP

AZD6140

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/s/

RAMESH K SOOD

05/13/2010

Memo of TCON

Application: NDA 022433
Sponsor: Astra-Zeneca
Drug: ticagrelor
Type of Meeting: TCON
Date of Meeting: May 11, 2010

List of FDA Meeting Participants:

Rob Fiorentino, MD	Medical Officer
Patricia Harlow, PhD	Pharmacology Acting Team Leader
Elizabeth Hausner, DVM	Pharmacology
Chhagan Tele, PhD	CMC
Mike Monteleone	Project Management

List of Sponsor Attendees:

Alex Gold	Development Brand Leader
Mark Hindle	Senior Project Scientist, Development
Jay Horrow	Exec Dir Med Science, Clinical
Mike O'Donovan	Director of Genetic Toxicology
Charles Humfrey	Preclinical Scientist
Scott Boyer	Chief Scientist and Head, Comp Tox Global Safety Assessment
Maria Edebrink	Team manager, Development
David Stong	Preclinical Scientist
Emery Gigger	Regulatory Affairs Director
Mary Whealy	Global Regulatory Lead
Judith Prosser	Regulatory Affairs Manager

Background: The Division requested an informal TCON with the sponsor of NDA 022433 ticagrelor to discuss the specification limits for impurity (b) (4) which came up positive in the computational genotoxicity databases. The sponsor sent a brief outline of their position via email prior to the meeting (attached).

Discussion: Dr. Hausner outlined that because the sponsor had no experimental data on (b) (4) the Division submitted it for a computational genotoxicity analysis. This analysis was positive with two alerts, one for bacterial mutagenicity and one for mouse lymphoma. The sponsor argued that because the impurity was structurally similar to ticagrelor, which, though positive in computational genotox analysis, had been shown to be negative through genotoxicity assays, AZ had concluded that alerts for (b) (4) were also false. Dr. Hausner responded that the basis for the SAR work is that small changes in structural details can profoundly affect activity and properties and that absent experimental data on (b) (4) the information in hand suggests genotoxicity.

The sponsor proposed that the Division submit both ticagrelor and (b) (4) for another computational analysis. After the meeting Dr. Hausner submitted ticagrelor only for analysis to avoid introducing bias in its analysis. After the meeting the Division requested the sponsor provide us with calculations of exposure in the toxicology studies as the content of (b) (4) is typically listed as (b) (4)

Reviewed

MMonteleone	17 May 2010
EHausner	18 May 2010
PHarlow	18 May 2010

Attachment: Sponsor background for TCON sent via email 5/10/2010

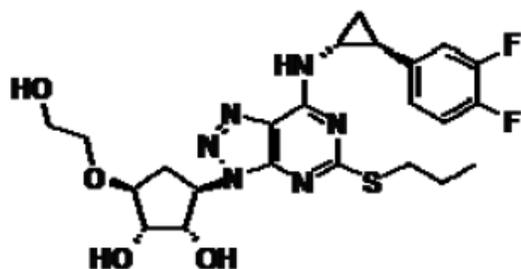
NDA 22-433 Ticagrelor Tables
Background Information for May 11, 2010 Teleconference
May 10, 2010 – Page 1 of 1

AstraZeneca wishes to provide further information in advance of the teleconference requested by the Agency on May 11, 2010 to discuss the impurity (b) (4) in ticagrelor drug substance.

- Ticagrelor has been shown to be negative in the Ames, mouse lymphoma and rat micronucleus assays.
- (b) (4) has not been tested in any genotoxicity assays.
- Ticagrelor has been found to be negative in genotoxicity assays although it showed an alert for (b) (4) in AstraZeneca's initial QSAR MCASE analysis (2006) but not DEREK.
- The structure of (b) (4) is similar to that of ticagrelor and showed a similar alert (b) (4) in the initial AstraZeneca QSAR MCASE analysis but not in the currently used versions of DEREK and MCASE. The structures are provided below.
- The addition of the (b) (4) does not raise any unique concerns for genotoxicity compared to the (b) (4) alone.
- Given the structural similarity to ticagrelor for the impurity and the lack of any genotoxicity signal for ticagrelor, AstraZeneca concludes that the initial alert for (b) (4) was shown to be false.

Can the Agency clarify which database highlighted the concern for (b) (4) and can they indicate the result that was obtained for ticagrelor in the same database?

Structures of ticagrelor and (b) (4)



Ticagrelor



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

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/s/

MICHAEL V MONTELEONE
05/18/2010

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO:
CDER-DDMAC-RPM

FROM: (Name/Title, Office/Division/Phone number of requestor)
Mike Monteleone, RPM DCRP x61952

REQUEST DATE
4-19-2010

IND NO.

NDA/BLA NO.
022433

TYPE OF DOCUMENTS
(PLEASE CHECK OFF BELOW)

NAME OF DRUG

Brilinta (b) (4)

PRIORITY CONSIDERATION

Standard

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
(Generally 1 week before the wrap-up meeting)

July 28, 2010

NAME OF FIRM:

AstraZeneca

PDUFA Date: September 16, 2010

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:

(Check all that apply)

- PACKAGE INSERT (PI)
- PATIENT PACKAGE INSERT (PPI)
- CARTON/CONTAINER LABELING
- MEDICATION GUIDE
- INSTRUCTIONS FOR USE (IFU)

TYPE OF APPLICATION/SUBMISSION

- ORIGINAL NDA/BLA
- IND
- EFFICACY SUPPLEMENT
- SAFETY SUPPLEMENT
- LABELING SUPPLEMENT
- PLR CONVERSION

REASON FOR LABELING CONSULT

- INITIAL PROPOSED LABELING
- LABELING REVISION

EDR link to submission:

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS:

Mid-Cycle Meeting: [April 14, 2010]

Wrap-Up Meeting: [August 4, 2010]

SIGNATURE OF REQUESTER
Michael Monteleone

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

- eMAIL
- DARRTS
- HAND

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

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/s/

MICHAEL V MONTELEONE
04/19/2010



NDA 022433

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, Delaware 19803

ATTENTION: Emery Gigger
Director, Regulatory Affairs

Dear Mr. Gigger:

Please refer to your New Drug Application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor Tablets 90 mg.

We also refer to your November 20, 2009, correspondence, received November 20, 2009, requesting review of your proposed proprietary name, Brilinta. We have completed our review of the proposed proprietary name, Brilinta and have concluded that it is acceptable.

The proposed proprietary name, Brilinta, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your November 20, 2009 submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Nina Ton, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at 301-796-1648. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Michael Monteleone at 301-796-1952.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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

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/s/

CAROL A HOLQUIST
02/18/2010



NDA 22-433

INFORMATION REQUEST

AstraZeneca
Attention: Emery Gigger, Director, Regulatory Affairs
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Dear Mr. Gigger:

Please refer to your November 13, 2009 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ticagrelor tablets.

We reviewed your dissolution data and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Provide the complete dissolution raw data, lot/batch number, the dissolution conditions used (apparatus, media, pH, rotation speed, volume), individual and average values of % of drug dissolved at each time point, f2 values (when making profile comparisons), and the manufacturing parameters ((b) (4)) used for the tested products.

The dissolution data should include, but not limited to the following categories:

- a. The data collected during formulation development.
- b. The data for the formulations used in Phases 1 and 2.
- c. The data for the Phase 3 and commercial formulations.
- d. The data for the formulations used in study 55 (the crossover 5-arm biostudy).
- e. The data for the formulation used in DoE's (Note that in some tables, the dissolution values at 45 minutes were reported. However, in this case, the data should include the values at the early time points also).
- f. The dissolution data for pilot batches and commercial batches so far.

The data should be tabulated in SAS transport file format.

If you have any questions, call Don Henry, Regulatory Project Manager, at (301) 796-4227.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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

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/s/

RAMESH K SOOD
01/26/2010



NDA 022433

FILING COMMUNICATION

AstraZeneca LP
Attention: Emery Gigger
Regulatory Affairs Director
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803

Dear Mr. Gigger:

Please refer to your new drug application (NDA) dated November 13, 2009, received November 16, 2009, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for Brilinta, (ticagrelor) 90 mg tablets.

We also refer to your submissions dated November 20, 24, 25 and December 8, 16, 18 (2), 22 and 24, 2009.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed January 15, 2010, 60 days after the date we received your application in accordance with 21 CFR 314.101(a). The review classification for this application is **Standard**. Therefore, the user fee goal date is September 16, 2010.

We acknowledge your request for a priority review but have determined not to grant your request for the following reasons:

A priority review is assigned if "Preliminary estimates indicate that the drug product, if approved, has the potential to provide, in the treatment, prevention, or diagnosis of a disease, one of the following: (1) safe and effective therapy where no satisfactory alternative therapy exists; or (2) a significant improvement compared to marketed products (approved, if approval is required), including *nondrug* products or therapies." The proposed labeling for ticagrelor states that it "as compared to clopidogrel has been shown to decrease the rate of a combined endpoint of cardiovascular death, MI or stroke. The difference between treatments was driven predominantly by CV death and MI with no difference on strokes." While decreasing CV death may be viewed as a significant improvement justifying a priority review, three factors support assignment of a standard review: (1) Nominal superiority of ticagrelor to clopidogrel was not evident in the U.S. subpopulation. The submission provides evidence of a possible treatment interaction with higher doses of aspirin used in the U.S. population, suggesting that ticagrelor could be inferior to clopidogrel when given on a background of higher dose aspirin. Potential confounders in the U.S. subpopulation and higher-dose aspirin subgroups need further

exploration. (2) Ticagrelor also appears to be associated with additional adverse effects compared to clopidogrel, including dyspnea and ventricular pauses. Given these efficacy and safety issues, our preliminary estimates suggest that ticagrelor may not be a significant improvement over clopidogrel when used with higher doses of aspirin. (3) There exists an adequate alternative therapy: The superiority of ticagrelor to prasugrel, another thienopyridine also approved for ACS indication, has not been demonstrated.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by July 30, 2010.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indications in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full waiver of pediatric studies for this application. Once we have reviewed your request, we will notify you if the full waiver request is denied and a pediatric drug development plan is required.

If you have any questions, please call Michael Monteleone, Regulatory Project Manager, at (301) 796-1952.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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/s/

NORMAN L STOCKBRIDGE
01/05/2010