CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 202155/ S-13

Trade Name: **ELIQUIS**

Generic Name: Apixaban

Sponsor: Bristol Myers Squibb

Approval Date: 05/03/2016

Indications: ELIQUIS is a factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy.

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APPLICATION NUMBER:

NDA 202155/ S-13

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155/S-013

APPROVAL LETTER

Bristol-Myers Squibb Company
Attention: Diptee Gajjar, B.Pharm, Ph.D.
Director, Global Regulatory Lead, Global Regulatory & Safety Sciences
P.O.Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gajjar:

Please refer to your Supplemental New Drug Application (sNDA) dated and received November 30, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eliquis (apixaban) 2.5 mg and 5 mg Tablets.

This "Changes Being Effected in 30 days" supplemental new drug application provides to add Bristol-Myers Squibb's facility in Humacao, Puerto Rico as a Packaging Site for apixaban Tablets.

We have completed our review of this supplemental new drug application. This supplement is approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Maryam Changi, Regulatory Business Process Manager, at (240) 402-2725.

Sincerely,

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300396790, cn=Wendy I. Wilson -S
Date: 2016.05.03 09:29:27 -04'00'

Wendy Wilson-Lee, Ph.D.
Branch Chief, Branch 1 (Acting)
Division of New Drug Product 1
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202155/ S-13

CHEMISTRY REVIEW(S)

DIVISION OF NEW DRUG PRODUCTS I
NDA 202155, S-013
REVIEW OF CHEMISTRY, MANUFACTURING, AND CONTROLS

NDA #: 202155 **DATE REVIEWED:** 05/02/16

OND: Division of Cardiovascular and Renal Drug Product

REVIEW #: 1 **REVIEWER:** Sherita McLamore-Hines, Ph.D.

SUBMISSION TYPE:
CBE-30 Supplement

CDER DATE:
12/18/2015

NAME & ADDRESS OF APPLICANT:
Applicant: Bristol-Myers Squibb (BMS)
P.O. Box 4000
Princeton, NJ 08543

Representative: n/a

DRUG PRODUCT NAME:
Proprietary: ELIQUS™
Established: apixaban

PHARMACOL. CATEGORY/INDICATION: Treatment of Acute Coronary Syndrome (ACS)

DOSAGE FORM: Film Coated Tablets

STRENGTHS: 2.5 mg and 5 mg

ROUTE OF ADMINISTRATION: Oral

Rx/OTC: *Rx*

SPECIAL PRODUCTS: ____Yes xx No

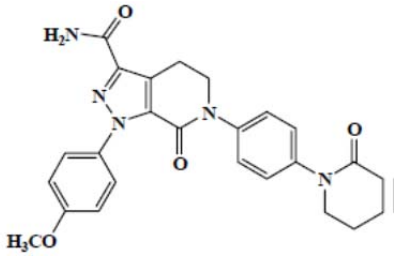
CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name: 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxo-1-piperdinyl)phenyl], 4,5,6,7-tetrahydro-1*H*-Pyrazolo[3,4-*c*]pyridine-3-carboxamide

Molecular Formula: $C_{25}H_{25}N_5O_4$

MW: 459.50

Chemical Structure:



SUPPLEMENT PROVIDES FOR: ELIQUIS™ (apixaban) 2.5 and 5 mg film coated tablets are currently manufactured and released tested by BMS of Humacao, PR and BMS of Mt. Vernon, IN. The approved packaging sites are BMS of Mt. Vernon (blisters and bottles), BMS of Frosinone, Italy (blisters and bottles) and [redacted] (b) (4). This supplement provides for the addition of the BMS site in Humacao, PR as an additional packaging site for the drug product (bottles only). There are no other changes are included in this supplement. No additional information is provided to support this change.

CONSULT: n/a

SUPPORTIVE DOCUMENT: None

CONCLUSION: While SUPAC-IR does not address the addition of a new packaging site, according to the FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics, Oral Tablets and Capsules are of low packaging concern as the likelihood of packaging components interacting with the packaging is low. Moreover, because the container closure system has proven to be suitable for the intended use and the proposed site is currently approved for manufacturing, packaging and testing the drug product, the reviewer is confident that the risks associated with the addition of the Humacao, PR as a drug product packaging site are insignificant. Accordingly, the applicant has provided adequate information to support the addition of BMS of Humacao, PR as an additional packaging site for ELIQUIS™ (apixaban) 2.5 and 5 mg film coated tablets. The applicant was asked to commit to placing one batch of each strength of the drug product packaged at the new site on stability. The applicant responded affirmatively and indicated that the results would be reported in the NDA annual report. Accordingly, we recommend that this application be APPROVED.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 202155/ S-13

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

From:	Kord Bacheh Changi, Maryam
To:	"diptee.gajjar@bms.com"
Subject:	CMC Information Request sNDA 202155/S-13
Date:	Monday, April 25, 2016 4:21:00 PM
Attachments:	image003.png
Importance:	High

Dear Dr. Gajjar,

We are reviewing the CMC portion of sNDA 202155/S-013 and have the following information requests:

- *Commit to placing one batch of each strength of the drug product packaged at the Humacao, PR site on stability. The stability results for the new packaging site are annual reportable.*

Please submit your response as an amendment to your application. Please also submit a copy to me via email by April 29, 2016.
Please kindly confirm the receipt of this email

Thank you,

Maryam Changi, PharmD,
RBPM, Office of Program and Regulatory Operations (OPRO)
Office of Pharmaceutical Quality/CDER/FDA
Phone:(240) 402-2725
Email: Maryam.Kordbachehchangi@fda.hhs.gov

Kord Bacheh Changi, Maryam

From: Wilson, Wendy
Sent: Wednesday, December 09, 2015 2:38 PM
To: Kord Bacheh Changi, Maryam
Subject: RE: Two new Supplement Triage form NDA 202155/S-013 and (b) (4)

Oh, ok. I didn't catch that either.

(b) (4)

202155 can remain a CBE-30 if the site is in good standing. It is an immediate release product so it can be a CBE.

Wendy

From: Kord Bacheh Changi, Maryam
Sent: Wednesday, December 09, 2015 2:27 PM
To: Wilson, Wendy
Subject: RE: Two new Supplement Triage form NDA 202155/S-013 and (b) (4)

Hi Wendy,

202155/S-013 is a CBE-30..... I upgrade it to PAS
(b) (4)

I apologize, I think in my email below I miss- categorize them.

Just confirm that above changes are ok!

Maryam

From: Wilson, Wendy
Sent: Wednesday, December 09, 2015 2:19 PM
To: Kord Bacheh Changi, Maryam
Cc: Sapru, Mohan; McLamore-Hines, Sherita; Chelliah, Mariappan
Subject: RE: Two new Supplement Triage form NDA 202155/S-013 and (b) (4)

Hi Maryam

Sorry for the delay on these.

202155/S-013 will **remain a PAS** and the assigned product quality reviewer will be **Sherita will be the reviewer.**

(b) (4)

Let me know if you need anything additional.

Thanks.

Wendy

From: Kord Bacheh Changi, Maryam
Sent: Wednesday, December 02, 2015 11:56 AM
To: Wilson, Wendy
Cc: Sapru, Mohan
Subject: Two new Supplement Triage form NDA 202155/S-013 and (b) (4)

Hi Wendy,

Attached, please find two additional Supplements Triage forms for NDA 202155/S-013 (**PAS)** and (b) (4) (b) (4) Please let me know when IQA is ready for them.

Thanks,

Maryam

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202155/S-013

CBE SUPPLEMENT – ACKNOWLEDGEMENT

Bristol-Myers Squibb Company
Attention: Sekayi Mushonga, Pharm.D.
Director, US Regulatory Liaison CV & Metabolics
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Mushonga:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 202155

SUPPLEMENT NUMBER: S-013

PRODUCT NAME: Eliquis (apixaban) Tablets

DATE OF SUBMISSION: November 30, 2015

DATE OF RECEIPT: November 30, 2015

This supplemental application, submitted as a "Changes Being Effected in 30 days" supplement, proposes the following change(s): Packaging site transfer from Mt Vernon to Humacao in Puerto Rico.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on January 29, 2016 in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be May 30, 2016.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following 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

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (240) 402-2725

Sincerely,

Maryam Changi, Pharm.D
Regulatory Business Process Manager
Office of Program and Regulatory Operation
Office of Product Quality
Center for Drug Evaluation and Research