Lupin Inc.

January 26, 2024

VIA ELECTRONIC SUBMISSION

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration (HFA-305)
5630 Fishers Lane, Room 1061
Rockville, MD 20852

SUITABILITY PETITION

Dear Sir or Madam:

The undersigned petitioner submits this petition, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act ("FD&C Act"), and in accordance with 21 C.F.R. § 10.20 and 21 C.F.R. § 10.30 requesting the Commissioner of the Food and Drug Administration ("FDA") to declare that the proposed drug product Apixaban Oral Suspension, 1.25 mg/mL is suitable for consideration in an Abbreviated New Drug Application ("ANDA").

I. ACTION REQUESTED

The petitioner requests that the Commissioner of the FDA declare that the proposed drug product, Apixaban Oral Suspension, 1.25 mg/mL is suitable for submission as an ANDA. The listed reference drug product (RLD), upon which this petition is based, is ELIQUIS® (apixaban) Tablets, 2.5 mg and 5 mg, by Bristol-Myers Squibb, NDA #202155.

II. STATEMENT OF GROUNDS

The FD&C Act § 505(j)(2)(C) provides for the submission of an ANDA for a drug product that differs in dosage form from that of the listed drug provided the FDA has approved a petition that proposed filing such an application.

The RLD ELIQUIS® by Bristol-Myers Squibb is an oral tablet product containing either 2.5 mg or 5 mg of apixaban. The petitioner hereby seeks approval of a change in dosage form from a tablet to an oral

suspension with a strength of 1.25 mg/mL. The proposed strength will permit patient dosing consistent with approved labeling for the RLD as a 2 mL dose of the proposed product will be equivalent to the 2.5 mg strength of ELIQUIS® Tablets and a 4 mL dose will be equivalent to the 5 mg strength of ELIQUIS® Tablet. The proposed Apixaban Oral Suspension, 1.25 mg/mL product will be packaged in 75 mL, 100 mL, and 150 mL amber bottles and a graduated dosing syringe will be provided to ensure accuracy of the delivered dose. Availability of Apixaban Oral Suspension, 1.25 mg/mL in 75 mL, 100 mL and 150 mL bottles will permit practitioners to prescribe the appropriate bottle size based on the required dose for the patient's condition and duration of therapy consistent with approved labeling for the RLD. The ANDA will include a bioequivalence study to establish bioequivalence of the proposed oral suspension to ELIQUIS® tablets. Furthermore, the proposed product will include all currently approved conditions of use for ELIQUIS® Tablets. Establishing bioequivalence of the proposed product to the RLD while being labeled for all conditions of use will permit the proposed product to rely upon FDA's previous finding of safety and efficacy for ELIQUIS® and should obviate any concerns from FDA related to the safety or efficacy of the proposed change in dosage form.

Availability of an Oral Suspension dosage form will aid in the administration of this product to patients that have difficulty swallowing or otherwise are unable to swallow whole tablets. Labeling for the RLD ELIQUIS® provides instructions for medical providers and/or patients (see Section 2.6 of ELIQUIS® Label) to prepare a suspension in water, D5W, or apple juice after the tablets are crushed. Crushed tablets can also be mixed with applesauce and promptly administered. Prepared suspensions of ELIQUIS® may also be administered via nasogastric tube. Once crushed and either mixed with applesauce or prepared as a suspension, the resulting preparation is only stable for 4 hours. Because ELIQUIS® is administered twice daily for each of its approved indications, patients or medical providers are only able to prepare a single dose due to the limited 4-hour stability of the crushed tablet. Availability of Apixaban Oral Suspension would provide greater convenience for these patients, greater assurance of the correct delivered dose, assurance of uniform and even particle size distribution in the suspension when compared to crushed tablets, and reduce burden on care givers in practice settings such as nursing homes or other assisted care facilities that currently crush ELIQUIS® tablets for patients that are unable to swallow whole tablets or those with dysphagia.

Dysphagia is increasingly common in older adults and occurs in 11–14% of adults ≥ 65 years of age. Dysphagia is also a common occurrence following stroke. A systematic literature review showed that 64–78% of patients who were treated in acute and long-term care facilities after experiencing a stroke experienced dysphagia.[1] Patients with dysphagia may delay taking medication or skip the medication

[1] Blaszczyk, Amie, et al. "Crushed Tablet Administration for Patients with Dysphagia and Enteral Feeding:Challenges and Considerations," *Drugs & Aging, vol. 40, no. 10, Oct. 2023 pp. 895-907.*

entirely and to mitigate such risk of non-compliance clinicians will often seek alternate methods of administration. Suboptimal adherence to apixaban therapy due to skipping doses is associated with a 39% higher risk of stroke.[2] The label of ELIQUIS® tablets also has a Black Box Warning stating "PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS". Thus, in patients who skip apixaban doses due to difficulty in swallowing tablets and prematurely discontinue therapy without an alternative anti-coagulant coverage are at increased risk of adverse clinical outcomes.

III. Pediatric Research Equity Act applicability

The proposed change in dosage form triggers the Pediatric Research Equity Act (PREA) which requires application sponsors to conduct studies in pediatric patients, if the Agency concludes that such studies would provide beneficial health data for the pediatric population. The Act specifically requires that a request for a new dosage form is subject to a pediatric evaluation. The Act also provides for a waiver from such requirement if the drug:

1. does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and
2. is not likely to be used in a substantial number of pediatric patients.

Approved labeling for ELIQUIS® does not contain any recommendations for use of this product in pediatric populations and Section 8.4 of the labeling contains the statement "Safety and effectiveness in pediatric patients have not been established." This statement has appeared in labeling for ELIQUIS® from the original approval granted by FDA on December 28, 2012, through the most recently approved labeling on October 12, 2021, associated with Supplement 034.

Approval letters posted on drugs@fda indicates that for the original approval granted on December 28, 2012, FDA waived PREA requirements for the approved indications subject to this approval: "We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease is rare in children"-See Original Approval letter provided as **Attachment 1**. FDA's PREA waiver applied to the indications approved at that time where "ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation".

[2] Ozaki, Aya F., et al. "Real-world Adherence and Persistence to Direct Oral Anticoagulants in Patients With Atrial Fibrillation: A Systematic Review and Meta-Analysis." *Circulation: Cardiovascular Quality and Outcomes, vol. 13, no. 3, Mar 2020.*

FDA subsequently granted another waiver of the PREA requirements when S-003 was approved on March 13, 2014 for ELIQUIS® where S-003 was approved "for a new indication for the prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement surgery." The approval letter for S-003 contained the following PREA waiver statement from FDA "We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable and there are too few children with this condition to study"-See Approval letter for S-003 provided as **Attachment 2.**

On August 21, 2014, FDA approved S-006 for ELIQUIS® where this approval provided for the new indication "for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and for the reduction in the risk of recurrent DVT and PE following initial therapy." Even though FDA previously waived PREA for the prophylaxis indication approved in the context of S-003 the approval letter for S-006 only deferred pediatric studies until August 30, 2020, in relation to these treatment indication for DVT and PE. A search of FDA's database for Post market Requirements and Commitments when inputting "apixaban" into the Product field and selecting the Pediatric Research Equity Act option results in two PREA related requirements where the Current Status for Requirement #1 is **Submitted** and the Current Status for Requirement #2 is **Delayed**. The final study report for Requirement #1 was submitted to FDA on December 10, 2020 and the final report for Requirement #2 now has a Projected Completion date of October 18, 2024. It is noted that the timelines for completion of Requirement #2 have been the subject of three extensions.

Petitioner hereby respectfully requests that FDA grant a waiver of the requirements to complete pediatric studies under PREA due to FDA's previous PREA waiver grants for the indications of "to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation" which were the original approved indications for ELIQUIS® and for the "prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE), in adult patients who have undergone hip or knee replacement surgery" which were approved in the context of S-003 on March 13, 2014. Petitioner requests a waiver of the pediatric study requirements under PREA "for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) and for the reduction in the risk of recurrent DVT and PE following initial therapy" which were approved in the context of S-006 as the proposed Apixaban Oral Suspension product will not represent a meaningful therapeutic benefit over existing therapies where those therapies are Pradaxa® Oral Pellets NDA 214358 and Xarelto® for Oral Suspension NDA 215859. Each of these products are available in a pediatric friendly dosage form and are adequately labeled for use of treatment of pediatric patients for Venous Thrombotic Events (VTE) an indication that encompasses both DVT and PE.

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IV. ENVIRONMENTAL IMPACT

The petitioner claims a categorical exclusion under 21 CFR 25.31.

V. ECONOMIC IMPACT

The petitioner will submit information on economic impact upon request by the agency if applicable.

VI. CERTIFICATION

The undersigned certifies, that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Sincerely,

Venkata S. Devarakonda

Digitally signed by Venkata S. Devarakonda
Date: 2024.01.26 07:42:04 -05'00'

Dr. Venkata S Devarakonda,
Sr. Manager, Regulatory Affairs.
Lupin Inc.

Please contact me at (443) 562-6070 (M) or email me at VenkataDevarakonda@lupin.com if you have any questions related to this petition.

Attachments accompanying this petition:

- Attachment 1: Copy of Original Approval letter for ELIQUIS® NDA #202155
- Attachment 2: Copy of Approval Letter for S-003 ELIQUIS® NDA #202155
- Attachment 3: Copy of the relevant excerpt from the current electronic Edition of the *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book) –
- Attachment 4: Current Package Insert for source RLD: Drugs@FDA
- Attachment 5: Draft Package Insert Proposed for Apixaban Oral Suspension, 1.25 mg/mL

References:

Blaszczyk 2023
Ozaki 2020