CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214358Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 214358

Review # 1

Drug Name/Dosage Form	Dabigatran etexilate oral pellets
Strength	20mg, 30mg, 40mg, 50mg, 110mg, 150mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Boehringer Ingelheim Pharma

SUBMISSIONS REVIEWED	DOCUMENT DATE
Original	09/21/2020
Quality Information	09/28/2020
Proprietary Name	11/06/2020
Quality Response to Information Request	01/08/2021
Labeling Information	01/14/2021
Labeling Information	01/27/2021

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Ben Zhang	Suong Tran
Drug Product	Dhanalakshmi Kasi	David Claffey
Process/ Facility	Alex Gontcharov	Steve Rhieu
Biopharmaceutics	Debasis Ghosh	Poonam Delvadia
Regulatory Business Process Manager	Grafton Adams	
Application Technical Lead	Dhanalakshmi Kasi	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. **DMFs: None**

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	022512	

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The final OPQ recommendation is for Approval.

II. Summary of Quality Assessments

A. Product Overview

Dabigatran etexilate oral pellets is developed for the treatment and reduction of risk of recurrence of venous thromboembolism in pediatric patients for children ages (b)(4) and < 12 years. The drug product is supplied in 20mg, 30mg, 40mg, 50mg, 110mg, 150mg. The drug product is administered immediately or within 30 minutes after mixing with rice cereal prepared with water, apple sauce, carrot mush, banana mush, or apple juice for 30 minutes at room temperature. This drug product is already approved as dabigatran etexilate mesylate capsules under NDA 022512 for the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients aged 8 to < 18 years. The dosage strengths are 75 mg, 110 mg, and 150 mg.

The information related to active pharmaceutical ingredient, dabigatran etexilate mesylate is covered mostly by NDA 022512. The applicant identified two polymorphs, (b) (4) and (b)(4) by x-ray diffraction measurement. (b) (4) is the desired form (b) (4) (b) (4) The acceptance criterion for (b) (4) is based on ICH M7 and the acceptance criterion for impurity (b) (4) (b) (4) is found acceptable from a toxicology perspective. The batch release data are adequate to support the use of drug substance in the manufacture of drug product pellets. The storage condition for the drug substance is (b) (4) and the proposed shelf life is (b) months. The drug substance reviewer is recommending approval.

The drug product pellets are manufactured by (b) (4) . All facilities appear adequate both in the experience in operations performed and in GMP compliance history.

The proposed dissolution method is same as the method approved for capsule formulation (NDA 022512). The proposed dissolution acceptance criterion (NLT (b)(4)%(Q) in 15 min) is based on clinical trial and primary stability batches and it is tighter than approved capsule formulation. The compatibility study demonstrated that the recommended fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

B. Quality Assessment Overview

Drug Substance

Dabigatran etexilate mesylate is a yellow-white or yellow crystalline powder with no chiral centers. It is practically insoluble in water, and the solubility increases with acidic pH. Most of the drug substance information is referenced to the approved information in NDA 022512. The difference between NDA 214358 and the previously approved NDA 022512 is with respect to polymorphism, degradant (b) (4) (b) (4) and an ICH M7 re-evaluation. The applicant identified two polymorphs, (b) (4), by x-ray diffraction measurement. (b) (4) is the desired form and it is controlled (b) (4) The impurity limit for degradant (b) (4) (b) (4) is (b) (4)% and Pharmacology Toxicology reviewer found this limit acceptable for the pediatric indication. The test limit for (b) (4) is re-evaluated as per ICH M7 for potential immunogenicity for pediatric dosing of up to (b) (4) mg. The limit of < (b) (4) ppm on (b) (4) (b) (4) in the drug substance specification would ensure the limit of < (b) (4) ppm in the drug product specification. Re-test period is (b) months when stored in (b) (4).

Drug Product

Dabigatran etexilate oral pellets is developed for the treatment and reduction of risk of recurrence of venous thromboembolism in pediatric patients for children ages (b) (4) and < 12 years. The drug product is supplied in 20mg, 30mg, 40mg, 50mg, 110mg, 150mg and administered immediately or within 30 minutes after mixing with rice cereal prepared with water, apple sauce, carrot mush, banana mush, or apple juice for 30 minutes at room temperature. The applicant developed the drug product based on the approved drug dabigatran etexilate hard capsules at dose strengths of 75 mg, 110 mg and 150 mg under NDA 022512. The maximum intake of all excipients has been evaluated from a toxicological perspective. The drug product is tested for appearance, identification, assay, impurities, (b) (4) (b) (4) uniformity of dosage units, dissolution and microbiological quality. (b) (4) (b) (4) Impurity (b) (4) (b) (4) is determined by Pharm/Tox to have an acceptable margin of safety for its use in the intended population and is considered qualified. The dabigatran etexilate (b) (4) pellets contained in packets are packaged additionally in an aluminum bag containing desiccant to guarantee an adequate drug product quality over the intended shelf life of 36 months at room temperature.

C. Special Product Quality Labeling Recommendations: None

***D.* Life Cycle Knowledge Information:** None

Application Technical Lead Name and Date: Dhanalakshmi Kasi, Ph.D.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with revisions provided below.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights	(b) (4)	
Proprietary name		Revised version: PRADAXA® (dabigatran etexilate) oral pellets
Established name(s)		
Route(s) of administration		
Dosage Forms and Strengths Heading in Highlights	(b) (4)	
Summary of the dosage form(s) and strength(s) in metric system.		Revised version: Oral Pellets: 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg per packet (3)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

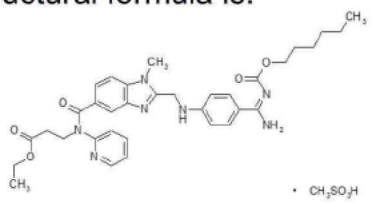
1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4)	PRADAXA oral pellets are available in the following strengths: • 20 mg yellowish pellets in a packet • 30 mg yellowish pellets in a packet • 40 mg yellowish pellets in a packet • 50 mg yellowish pellets in a packet • 110 mg yellowish pellets in a packet • 150 mg yellowish pellets in a packet
Strength(s) in metric system		
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		

Item		Assessor's Comments
DESCRIPTION:		
Proprietary and established name(s)	(b) (4)	PRADAXA contains dabigatran etexilate mesylate, a direct thrombin inhibitor. The chemical name of dabigatran etexilate mesylate is β-Alanine, N-[[2-[[[4-[[[(hexyloxy)carbonyl] amino]iminomethyl] phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-,ethyl ester, methanesulfonate and it has a molecular formula of $C_{34}H_{41}N_7O_5.CH_4O_3S$ and molecular weight of 723.86 for the mesylate salt and 627.75 for the free base. The structural formula is:  Dabigatran etexilate mesylate is a yellow-white to yellow powder. It is freely soluble in methanol, slightly soluble in ethanol, and sparingly soluble in isopropanol. A saturated solution in pure water has a solubility of 1.8 mg/mL.
Dosage form(s) and route(s) of administration		
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol		
Statement of being sterile (if applicable)		
Pharmacological/ therapeutic class		
Chemical name, structural formula, molecular weight		
If radioactive, statement of important nuclear characteristics.		

Other important chemical or physical properties (such as pKa or pH)	(b) (4)	PRADAXA are oral pellets contained in a packet. Each packet contains 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, or 150 mg equivalents of dabigatran etexilate supplied as 23.06 mg, 34.59 mg, 46.12 mg, 57.65 mg, 126.83 mg, or 172.95 mg dabigatran etexilate mesylate along with the following inactive ingredients: acacia, dimethicone, hypromellose, hydroxypropyl cellulose, talc, and tartaric acid.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	None.	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	None.	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section	(b) (4)	
Available dosage form(s)		PRADAXA oral pellets are yellowish pellets in a silver-colored, child-resistant packets. The packets are placed in an aluminum bag with a (b) (4) (b) (4) desiccant.
Strength(s) in metric system		PRADAXA oral pellets are supplied as follows:
Available units (e.g., bottles of 100 tablets)		
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number		
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Store in the original package to protect from moisture. Do not open the packets until ready for use. Use the PRADAXA oral pellets within 6 months of opening the aluminum bag containing the packets.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		

Strength	Package	NDC
20 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0425-78
30 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0430-18
40 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0435-96
50 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0440-53
110 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0445-87
150 mg	unit of use carton with 1 aluminum bag containing 60 packets	0597-0450-16

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	See above.	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	No Information included.	

1.2.3 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed by: Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT 06877 USA PRADAXA is a registered trademark of and used under license from Boehringer Ingelheim International GmbH. Copyright 20xx Boehringer Ingelheim Pharmaceuticals, Inc. ALL RIGHTS RESERVED	Adequate

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

No Information included.

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Dhanalakshmi Kasi

Digitally signed by Dhanalakshmi Kasi
Date: 2/04/2021 03:54:21PM
GUID: 53150dea000054615f30e13bde0d487c

David Claffey

Digitally signed by David Claffey
Date: 2/04/2021 05:18:53PM
GUID: 508da71e00029e20b201195abff380c2

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	Boehringer submitted an NDA under 5050(b)(1) for Pradaxa® (Dabigatran Etexilate) Pellets 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg as a treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients.
NDA Number	214358
Assessment Cycle Number	1
Drug Product Name/ Strength	Pradaxa® ((Dabigatran Etexilate) Pellets 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, 150 mg
Route of Administration	Oral
Applicant Name	Boehringer Ingelheim Pharmaceuticals, Inc.
Therapeutic Classification/ **OND Division**	Division of Non-Malignant Hematology
RLD/RS Number	Not applicable
Proposed Indication	Treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients aged less than 12 years (b) (4)

Assessment Recommendation: *Adequate*

Assessment Summary:

Boehringer Ingelheim Pharmaceuticals ('applicant') submitted (09/21/2020) an original NDA under 505(b)(1) seeking marketing approval for Pradaxa pellets, a new dosage form for dabigatran etexilate mesylate for the treatment and prophylaxis of venous thromboembolism in pediatric patients aged less than 12 years old (b) (4) l. The applicant indicated that Pradaxa (dabigatran etexilate mesylate) capsule was originally approved by the Agency on 10/19/2010 to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation. The proposed drug product is the (b) (4) . The applicant cross-referenced all applicable CMC information to NDA 022512[1].

[1] NDA214358 (214358 - 0002 - (3) - 2020-11-06 - ORIG-1 /Proprietary Name/Request for Review) - Cross-reference to other applications (0000)

The drug substance is practically insoluble in water and it exhibits pH dependent solubility: 10 mg/mL at pH 1 and <10 µg/mL at pH>5).[2] The proposed product (pellets in sachets) is designed as age-appropriate formulation intended to be used for the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients aged less than 12 years. The proposed drug product (pellets) is available in six dose strengths (20 mg, 30 mg, 40 mg, 50 mg, 110 mg and 150 mg) to increase dosing flexibility (single sachet per dose or in a combination of up to three sachets from dose strengths with a maximum daily dose of (b) (4) mg). The pellets in sachets are intended to be mixed with (b) (4) of soft foods/juices before oral administration. Since the pellets (NMT (b) (4) mm) are well below the FDA recommended size (NMT 2.8 mm) of beads in drug product labeled for sprinkle, the proposed drug product can be swallowed without chewing.

Following is a cross-section drawing of granule (pellet) which contains (b) (4) . The (b) (4) in pellet is (b) (4) %.

Fig 1. Structure of dabigatran Etexilate Pellets as submitted in Sec 3.2.P.2 Pharmaceutical Development Fig 2.

Biopharmaceutics review is focused on the assessment of the dissolution method and acceptance criterion for routine quality control of the (b) (4) (pellets) at release and stability including the effect of co-administered fluids/soft-food on the performance of in vitro dissolution.

The proposed dissolution method is same as the method approved for capsule formulation (NDA 022512). (b) (4) . While the method does not discriminate critical material attributes of drug substance (particle size, polymorphism), it can detect changes to the product under stress conditions (high humidity, heat etc.). Despite its limited discriminatory power, as a legacy method, it is acceptable as a routine QC dissolution method. The pellets are (b) (4) (b) (4) containing pellets (NDA 022512). The proposed dissolution acceptance criterion (NLT (b) (4) %(Q) in 15 min) is tighter than approved capsule (containing pellets) formulation. The proposed acceptance criterion is based on clinical trial and primary stability batches. Essentially, at the 15 min time point the (b) (4) the pellet is sufficiently dissolved which reflects a drug product with very rapid dissolution in the proposed QC media.

[2] NDA214358 (214358 - 0002 - (3) - 2020-11-06 - ORIG-1 /Proprietary Name/Request for Review) - Pharmaceutical Development (q00258093-02)

Table 1. Approved Dissolution Method and Acceptance Criterion

Source	USP Apparatus	Speed	Medium	Temperature	Volume (mL)	Proposed and approved Acceptance Criterion
In-House	I (Basket)	100 rpm	0.01M HCl (pH 2.0)	37°C	900 mL	NLT (b)(4)%(Q) in 15 min

Since pellets are designed for oral administration after mixing with soft food/juice, food-compatibility study was performed to assess the impact of the co-administered fluid/soft-food on in vitro dissolution of the product. The dissolution method for compatibility testing was modified to enable distribution of the food-pellet mixture within the dissolution vessel, and to avoid interference of the foods in the quantification of the drug substance. Hence, USP apparatus II (paddle) was used for food-compatibility study in lieu of USP Apparatus I (basket). Other dissolution parameters (0.01M HCl, pH 2.0, 900 mL, 37°C) are the same as the proposed for QC method. The method was validated for the intended use. It has been noted that the recommended dissolution media like 0.1N HCl[3] is not appropriate for this product due to poor acidic solution state stability of drug substance. The dissolution of drug substance from the mixture of drug product and food (juice/soft food), in most cases, is largely rapid ((b)(4)%) in 15 min in 0.01M HCl (QC media). Based on dissolution data from food compatibility study, no changes to dissolution was observed when the pellets were mixed with rice cereals (prepared with water), apple sauce, carrot mush, and apple juice even after 2h. While an in-use time-dependent decrease (after 30 min) in dissolution was observed for banana mush but it still met the proposed dissolution specification (> (b)(4)% in 15 min). The strawberry jam has a measurable effect on in vitro dissolution and failed to meet the dissolution criteria. Based on the above observation, in the proposed package insert, the applicant stated that "*administer Pradaxa pellets immediately or within 30 minutes after mixing. Do not give Pradaxa pellets if the pellets have been in contact with the soft food or apple juice for more than 30 minutes.*" From a biopharmaceutics perspective, the above statement is supported by dissolution data for food compatibility study. In absence of in vivo data, however, the overall effect of strawberry jam can't be established with in vitro dissolution data. Hence. strawberry jam is not recommended as a soft-food for this product. Overall, the compatibility study demonstrated that co-administered recommended (see package insert) fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

[3] Use of liquids and/or soft foods as Vehicles for drug administration: General Considerations for selection and in vitro methods for product quality assessments – Guidance for Industry (July 2018). https://www.fda.gov/media/114872/download

Risk Assessment for Dissolution:

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle #	Comments
Particle size of API	Medium	Particle size of API is controlled by (b) (4) (b) (4)	Low	The acceptance criterion for API particle size is: (b) (4)
Polymorphic Form of API	Medium	API is manufactured as (b) (4) (b) (4) (b) (4) and it is controlled by (b) (4) (b) (4) (b) (4)	Low	The acceptance criterion for polymorphic form in API is: NMT (b) (4) % (b) (4)
Polymorphic purity for drug product (pellets)	Medium	Consistent with the specifications for the approved capsule strengths, testing for polymorphic purity for (b) (4) granules in sachets is not required because the two polymorphic forms have been demonstrated as bioequivalent (in vivo study) in approved capsules.	Low	See cross-referenced NDA 022512 for additional information.
Soft food/Juice vehicle for drug product (pellets)	Medium	Based on food compatibility study, the effect on dissolution is minimal when the product is mixed with recommended soft-food/juice before oral administration within 30 min (in-use period).	Low	See evaluation of Food compatibility study in the review document.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original Application (SR#0000)	09/21/2020

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): Not applicable

B.1 BCS DESIGNATION

Assessment: The Applicant does not request a BCS designation in this application therefore BCS classification is not evaluated. Based on information provided in cross-referenced NDA 022512, the applicant designated dabigatran etexilate as BCS Class 2 drug substance[4].

Solubility: The drug substance (dabigatran etexilate mesilate) is practically insoluble in water. The aqueous solubility is dependent on the pH of the respective medium with high solubility at low pH (more than 10 mg/mL at pH 1), but low solubility (< 10 µg/mL) at a pH of 5 and above. (b) (4) . Please note that pH 2 was selected as the QC dissolution medium. (b) (4)

Permeability: No permeability data provided in this submission. Based on the information provided in the cross-referenced NDA 022512, dabigatran etexilate free base is a highly permeable drug.

Dissolution: See Biopharm review below.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: {Adequate/Inadequate}

Dissolution Method:

[4] NDA022512 (022512 - 0456 - (2351) - 2020-11-20 - SUPPL-41 (Efficacy) /Clinical/Response To Information Request) - Pharmaceutical Development (U09-2017-01)

Dissolution method is cross-referenced to NDA 022512 which was approved for PRADAXA (dabigatran etexilate) Capsule [redacted] (b) (4) Following dissolution method was approved for capsule:

Table 2. Approved Dissolution Method (NDA 022512)

Source	USP Apparatus	Speed	Medium	Temperature	Volume (mL)
In-House	I (Basket)	100 rpm	0.01M HCl (pH 2.0)	37°C	900 mL

Above dissolution method was selected as a starting point for the development of dissolution method for pellets.

[redacted] (b) (4)

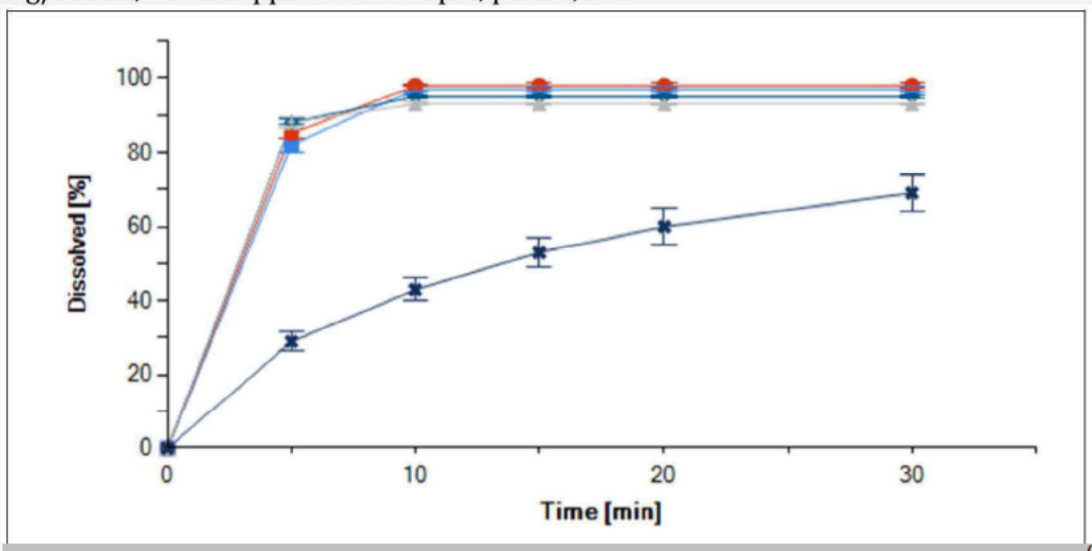
[5] NDA214358 (214358 - 0002 - (3) - 2020-11-06 - ORIG-1 /Proprietary Name/Request for Review) - Justification of Dissolution Specification (q00272337-01)

(b) (4)

[redacted]

- **Discriminatory Power of the Method**: The method was approved for capsule formulation containing dabigatran etexilate pellets. While the method was found to be non-discriminatory towards polymorphic forms or particle size, it was approved as a routine quality control method for capsule (NDA 022512). Since the outcome of the studies for approved capsule formulation (capsule containing pellets) is considered valid for the proposed pellet drug products (pellets), the method was evaluated for its ability to detect changes that might occur in sachets maintained at different storage conditions. For example, under humidity stress conditions (30°C/75%RH, 150 mg, open storage, without primary packaging) dissolution of the drug product drops significantly.

Fig 3. Influence of storage conditions under humidity stress conditions (30°C / 75 % RH., 24 hours, without primary packaging), dabigatran etexilate (b) (4) granules, 150 mg/sachet; basket apparatus 100 rpm, pH 2.0, n=6



(b) (4)

- ***Dissolution Specification***: The dissolution specification is established based on clinical trial supply batches and primary stability batches. The proposed dissolution specification is: NLT (b) (4) %(Q) in 15 min.

Reviewer's Comment: Adequate.

The dissolution method is selected based on the approved dissolution method for Capsule (NDA 022512). (b) (4) . The method showed some discriminatory power with samples under high humidity conditions. Although, the method does not discriminate drug substance quality attributes like polymorphic forms and particle size. Nonetheless, the method appears to be adequate as a QC method. The pellets are (b) (4) (b) (4) compared to dissolution from capsule containing pellets. The proposed dissolution acceptance criterion (NLT (b) (4) %(Q) in 15 min) is tighter than capsule formulation and based on dissolution data using the proposed dissolution method for clinical trial & primary stability batches. It is acceptable.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

Assessment: N/A

B.4 APPLICATION OF DISSOLUTION/IVIVC IN QbD

Assessment: N/A

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol Dose Dumping*

Assessment: N/A

B.6 IN-VITRO SOFT-FOOD INTERACTION STUDY

Assessment: {Adequate/Inadequate}

Intended use: Per submission, the proposed product is intended to be used for the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients aged less than 12 years (b) (4).

Design of Food-Compatibility Study: Compatibility studies for dabigatran etexilate (b) (4) granules in sachets were performed with specified food products (rice cereal, apple sauce, carrot mush, banana mush, strawberry jam, and apple juice) to evaluate the pharmaceutical characteristics and compatibility of the preparation to be administered. The investigation was performed on one primary stability batch of dabigatran etexilate (b) (4) granules, 20 mg/sachet, previously stored for 24 months at 25°C/60 % RH in the proposed commercial container closure system ((b) (4) sachets inside an aluminum bag with desiccant). Dabigatran etexilate (b) (4) granules were mixed with about 10 g of specified food products, which is equivalent to the amount of about two teaspoons. Mixing of (b) (4) granules with apple juice was done with about 10 mL juice. Dabigatran etexilate (b) (4) granules were in contact with the specified foods for up to 2 hours (120 minutes) at room temperature. The samples were tested for description and pH (both for information), **dissolution** BIBR 1048, degradation products BIBR 1048, and assay BIBR 1048.

Dissolution Method for Food-compatibility Study: The analytical procedure for dissolution testing of dabigatran etexilate (b) (4) granules (pellets) in food is based on the proposed analytical procedure for the drug product, dabigatran etexilate (b) (4) granules (pellets) in sachets in terms of the applied dissolution medium. The applicant indicated that the procedure was modified to enable distribution of the food/pellet mix within the dissolution vessel, and to avoid interference of the foods in the quantification of drug

substance. Therefore, dissolution testing was performed applying Apparatus II (paddle) instead of Apparatus I (basket), and an HPLC method based on the proposed analytical procedure for assay/degradation testing for the drug product in presence of food. The method was developed and validated for the intended use. Following is the summary of dissolution procedure:

Fig 4. Description of Dissolution procedure as presented in Sec 3.2.P.2 Food Compatibility Table 12.

Parameter	Conditions
Apparatus	Ph. Eur. / USP / JP paddle method (Apparatus II), 50 rpm
Medium	0.01 M hydrochloric acid, pH 2.0, 900 mL, 37 °C
Determination	HPLC gradient system equipped with auto injector and UV detector; cooled autosampler, set at 8 °C C18 column (e.g. Inertsil ODS2; 5 µm; 125 x 4 mm), oven temperature controlled (45 °C) Binary gradient: Ammonium acetate buffer pH 4.4 / Acetonitrile Detection: UV absorbance at (b) (4) nm
Preparation of test solution	Without food: Place the contents of one sachet into the test vessel. Operate the apparatus (paddle) at 37 °C and 50 rpm. With food: Weigh about 10 g food (or pipette about 10 mL of apple juice) into a petri dish. Sprinkle one sachet on the food and stir it up until all (b) (4) granules are in contact with food. Remove 2 x 20 mL dissolution medium from the vessel. Then slurry the food / (b) (4) granules mixture with the 2 x 20 mL dissolution medium and transfer the mixture from the petri dish into the vessel. Operate the apparatus (paddle) at 37 °C and 50 rpm.

Dissolution Study Results: For rice cereal, apple sauce, carrot mush, and apple juice, all mean dissolution values were greater than or equal to (b) (4) % dissolved within 15 minutes over the entire 120 minute in-use period, as is the case for (b) (4) granules without food. Dissolution test results of (b) (4) granules in presence of these foods, therefore, show profile similarity to (b) (4) granules without food for all investigated in-use periods. For banana mush, profile similarity ((b) (4) % dissolved within 15 minutes) is only achieved up to an in-use period of 30 minutes, and after 60 and 120 minutes in-use period, profile similarity is not achieved. For strawberry jam, mean dissolution values did not reach (b) (4) % dissolved at the 15 minutes sampling time point for any in-use period. The results from the food compatibility study demonstrate suitable compatibility of dabigatran etexilate (b) (4) granules when mixed with either rice cereal (prepared with water), apple sauce, carrot mush, banana mush, or apple juice for 30 minutes at room temperature. The applicant indicated that "*strawberry jam has a measurable effect on results for dabigatran etexilate* (b) (4) *granules according to the in vitro methods based on the QC dissolution and*

assay methods. It is not known whether the in vitro results would correlate to in vivo results. Therefore, conservatively, it is not recommended to include strawberry jam in the selected foods for use in administering dabigatran etexilate (b) (4) *granules."*

Reviewer's Comment on Compatibility Study: The compatibility study was performed on the lowest strength in sachets (20 mg/sachet). The applicant reasoned that lowest dosage represents worst-case scenario in regard to (b) (4) . The other dosage strengths (30 mg, 40 mg, 50 mg, 110 mg and 150 mg/sachet) are not considered for compatibility testing. The applicant stated that as food is always available in excess and each pellet is in contact and surrounded with food, therefore, testing of the 20 mg dosage strength is considered representative for the other, higher dosage strengths as well. The use of 20 mg dose is reasonable.

We note that in lieu of USP I apparatus (basket) proposed for QC dissolution test, USP II apparatus (paddle) was used for the food compatibility study. The method was adapted to "*enable distribution of the food/pellet mix within the dissolution vessel, and to avoid interference of the foods in the quantification of drug substance.*" Other dissolution parameters (0.01M HCl, pH 2.0, 900 mL, 37°C) are the same as proposed for QC method. It has been noted that the recommended dissolution media[3] of 0.1N Hydrochloric Acid can't be used due to poor solution state stability of drug substance. The method has been validated for the intended use. The validation parameters include: specificity, linearity, range, accuracy, repeatability, and robustness.

Except strawberry jam, all other food articles (rice cereal prepared with water, apple sauce, carrot mush, banana mush or apple juice) were found to be compatible with dabigatran etexilate granules (pellets). Banana mush showed time-dependent decrease of dissolution (after 30 min), but all other foods did not show any trend after 2 h with the proposed product. Based on the above observation, 30 min time period was established as in-use period. A comparison of the dissolution profile for the original product with the drug mixed with the proposed vehicle using f2 similarity is not appropriate in this case since > (b) (4) % dissolution is accomplished in 15 min.

Overall, the compatibility study demonstrated that co-administered fluid/soft-food is not likely to have any effect on the in vitro dissolution performance of the product.

The labeling (package insert) indicates the in-use period of 30 min with rice cereals (prepared with water), mashed carrots, apple sauce, mashed banana and apple juice. From a biopharmaceutics perspective, the above statement is supported by food compatibility dissolution data. While the strawberry jam did not pass in vitro compatibility test, the clinical relevance of in vitro dissolution result can't be ascertained without any in vivo data. Nevertheless, the applicant did not include strawberry jam in the labeling as a soft food.

B.7 IN-VITRO RELEASE TESTING (IVRT) FOR SEMI-SOLID PRODUCTS

Assessment: N/A

B.8 IN-VITRO PERMEATION TESTING (IVPT) FOR TRANSDERMAL/TOPICAL PRODUCTS

Assessment: N/A

B.9 IN-VITRO DISSOLUTION TESTING FOR ABUSE-DETERRENT PRODUCTS

Assessment: N/A

B.10 IN-VITRO BE EVALUATION FOR PULMONARY PRODUCTS

Assessment: N/A

B.11 EXTENDED RELEASE DOSAGE FORMS –*Extended Release Claim*

Assessment: N/A

B.12 BRIDGING OF FORMULATIONS

Assessment: N/A

B. 13 BIOWAIVER REQUEST

Assessment: N/A

R. REGIONAL INFORMATION

Comparability Protocols

Assessment: {Adequate/Inadequate}

Post-Approval Commitments

Assessment: {Adequate/Inadequate}

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None

Primary Biopharmaceutics Assessor's Name and Date:
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02/09/2021

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