CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214358Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 063267

MEETING REQUEST-
WRITTEN RESPONSES

Boehringer Ingelheim Pharmaceuticals Inc.
Attention: Charles R. Mazzarella
Director, Regulatory Affairs
900 Ridgebury Road, PO Box 368
Ridgefield, CT 06877

Dear Mr. Mazzarella:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for dabigatran etexilate mesylate.

We also refer to your submission dated October 18, 2019 containing a meeting request. The purpose of the requested meeting was to discuss the proposed contents (b) (4) to meet requirements outlined in the FDA's June 22, 2019 Written Request and to include treatment of venous thromboembolism in pediatric patients in the PRADAXA label.

Further reference is made to our Meeting Granted letter dated October 29, 2019, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your November 14, 2019 background package.

If you have any questions, call Charlene Wheeler, Chief Project Management Staff, at (301) 796-1141.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Clinical Team Leader
Division of Hematology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure:

- Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: IND 063267
Product Name: dabigatran etexilate mesylate (BIBR 1048 MS)

Indication: Dabigatran etexilate is indicated for the treatment (b) (4) (b) (4) of recurrent venous thromboembolism in pediatric patients aged (b) (4) to less than 18 years
Sponsor Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Boehringer Ingelheim Pharmaceuticals, Inc. requested for a meeting to discuss the proposed contents (b) (4) to meet requirements outlined in the FDA's June 22, 2019 Written Request and to include treatment of venous thromboembolism in pediatric patients in the PRADAXA label.

2.0 QUESTIONS AND RESPONSES

Question 1: *Does the FDA concur with the Electronic Submission Plan (Appendix 1) which details criteria for case report forms, narratives, datasets (e.g. CDISC SDTM study datasets and legacy analyses datasets, reviewer's guides, define.xml and acrf.pdf), summary level clinical site data, programs and laboratory units to be included in the supplemental application?*

FDA Response to Question 1: Overall your proposed electronic submission plan is acceptable.

However, the FDA requests that an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, be prepared and submitted in the NDA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document," available at: http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf.

Provide sufficient comments, adequate bookmarks, and hyperlinks in the define file(s) to ensure efficient review.

Question 2: *The following summary documentation, specific to the pediatric indication, will be provided in Module 2 of NDA 022512 only:*

2.2 Introduction to summary
2.4 Nonclinical overview
2.5 Clinical overview
2.6 Nonclinical written and tabulated summaries

2.6.6 Toxicology written summary

2.7 Clinical summary

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods
2.7.2 Summary of Clinical Pharmacology studies
2.7.3 Summary of Clinical Efficacy [indication]
2.7.4 Summary of Clinical Safety
2.7.5 References
2.7.6 Synopses of individual studies

A new Module 2.3 Quality Overall Summary (QOS) will not be provided in NDA 022512; however, Module 2.3 - Quality Overall Summary (QOS) will be prepared (b) (4) *for the new pediatric dosage* (b) (4) *(pellets* (b) (4)

Does the Agency concur with the proposed contents of Module 2?

FDA Response to Question 2: Yes, we concur.

We recommend that you consider a pre-NDA meeting with the Agency to discus the topline efficacy and safety results from your pediatric program prior to NDAs/supplement NDA submissions.

Question 3: *The following formulations are planned to be marketed to support the proposed indication in pediatric patients:*

Formulation	***Age groups***
Capsules of 75, 110 and 150 mg dose strength	*Pediatric patients aged ≥ 8 years.*
Pellets mixed with food (6 different dose strengths)	*Pediatric patients aged < 12 years of age).*
(b) (4)	

As mentioned in Question 2, BI plans to submit a sNDA to the current capsule NDA 022512. BI also plans to submit (b) (4) *the pellet formulation* (b) (4) (b) (4) *which will incorporate, by cross reference, all applicable information (e.g. clinical trial reports, clinical and non-clinical summary documents, etc.) submitted to NDA 022512.*

The cross-referencing specific for Module 3 CMC is discussed in Question 9.

Does the FDA agree with BI's cross reference strategies (b) (4) *?*

FDA Response to Question 3: Yes, the plan for cross-referencing is acceptable.

Question 4: *The Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) for the pediatric supplemental NDA will fulfill all requirements of the text portion of the Integrated Summaries of Safety and Efficacy (ISS / ISE). BI proposes that the textual summaries (SCE/SCS) in Module 2.7, in conjunction with the supportive tables, listings, and figures provided as part of the Clinical Trial Reports and as part of the pooled analyses across trials in Module 5, will be used to constitute an adequate ISE/ISS. In the SCE/SCS, appropriate cross references will be made from the text, in-text tables and figures to the source data. Adequate hyperlinks will be included in-text in Module 2.7 that will take the reader directly to the corresponding table(s) and figure(s) in Module 5.*

Does the FDA concur that the SCE and SCS will meet the requirements for an ISE/ISS?

FDA Response to Question 4: Your proposal to split the ISS and ISE between Module 2 (SCS and SCE) and Module 5 is acceptable.

Question 5: *BI proposes not to submit a 4-month safety update since all submitted pediatric trials will be completed at the time of submission.*

Does the FDA Agree?

FDA Response to Question 5: Please clarify how long patients will have been followed for safety at the time of the submissions (b) (4)

(b) (4)

[redacted] (b) (4)

Does the FDA agree with this strategy?

FDA Response to Question 6: FDA will have to review the PK modeling exercise to confirm that other approved capsule strengths of dabigatran can be assigned to the age and weight group [redacted] (b) (4) Please submit the PK modeling report for Agency's review.

Question 7: *As per the FDA's June 22, 2019 Written Request the statistical analysis plan for studies and 1160.108 "must be submitted to and agreed upon by the Agency". The following individual trial SAP along with the pooled analysis SAP have been provided as follows:*

- *Study 1160.106 TSAP - Appendix 2*
- *Study 1160.108 TSAP - Appendix 3*
- *Pooled Analysis SAP - Appendix 4*

Does the FDA agree with the SAPs provided?

FDA Response to Question 7: For Study 106, you plan to test the primary endpoint based on 1-sided alpha o [redacted] (b) (4). In general, the FDA's traditional standard for efficacy claim based on hypothesis testing is at 1-sided alpha of 0.025. Whether the study has demonstrated substantial evidence for study drug's efficacy will ultimately be a review issue. [redacted] (b) (4) We recommend you [redacted] (b) (4) perform the subgroup analyses by age for all the primary and key secondary endpoints. We also recommend you propose a primary method and several sensitivity analyses for assessing the impact of the missing data and dropouts.

For the other two studies, where no hypothesis testing is planned, your proposal appears reasonable.

Question 8: [redacted] (b) (4) *An overview of the planned CMC documentation for each of the proposed new NDA submissions is provided in Section 11.3 for dabigatran etexilate pellets* [redacted] (b) (4) *of this briefing package. The proposed Module 3 Table of Contents for these applications are provided in Appendix 5 and Appendix 6, respectively.*

Based on the summary of information describing the organization of content for Module 3 for each of the corresponding NDA submissions, does FDA have any comments regarding the general organization and/or proposed content for Module 3?

FDA Response to Question 8: The general organization of Module 3 is reasonable.

Question 9: *The quality of drug substance used for the pediatric dabigatran etexilate pellets formulation is the same as that which is approved for Pradaxa Capsules. Therefore, (b) (4) dabigatran etexilate pellets) the CMC information for drug substance will be provided by cross-reference to approved NDA 022512 for Pradaxa Capsules since NDA 022512 is fully electronic and easily accessible to FDA Reviewers.*

(b) (4)

(b) (4)

(b) (4)

This change is relevant for drug substance used in the capsules and in the pellets formulations. (b) (4)

Additionally, as presented in the "supporting data" section (11.2), the findings of the ICH Q3D risk assessment will be implemented for the drug substance used across all drug products.

For completeness, a reference to NDA 022512 for drug substance information will be provided in Module 1.4 of each new NDA.

Does FDA agree with the proposed cross-referencing strategy for drug substance information?

FDA Response to Question 9: Yes, the cross-referencing proposal appears acceptable.

Question 10:

NDA 022512:
EBRs will not be provided for capsules as the strengths of capsules proposed for use in the pediatric population are the same as those approved for adults.

(b) (4)

While multiple strengths of this formulation will be proposed for registration (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg/sachet), only one (1) EBR from the primary stability batches for the 20 mg and one (1) EBR from the 150 mg dose strengths will be provided to cover the range of dose strengths. (b) (4) *Furthermore, the primary stability batches of this dosage form have been manufactured at the production scale and at the proposed commercial sites using the proposed manufacturing process for the commercial product.*

EBRs written only in (b) (4) *will be translated. Only the English translated copies will be submitted.*

The Certificate of Analysis (CoA) for the drug product batch (EBR batch) will be provided in 3.2.R (b) (4)

(b) (4)

(b) (4)

Question 11: *In the original NDA submission* (b) (4) *a data package consisting of 24 months data (25oC/60% r.h.) and 6 months data (40oC/75% r.h.) will be provided for the primary stability batches (20 mg, 30 mg, 40 mg, 50 mg, 110 mg, and 150 mg/sachet)*

Dabigatran etexilate pellets in sachets are packaged in a secondary protective bag with desiccant. They are stored and tested according to a bracketed design, with full testing of three batches each for the lower dosage strengths of 20 mg, 30 mg, 40 mg/sachet, as they represent the worst case scenario with regard to (b) (4) (b) (4) *Full testing on three batches is also performed on the 150 mg/sachet dosage strength to cover the highest dosage in the bracketing design.*

For the 50 mg and 110 mg/sachet dosage strengths, a comparable stability performance to the other dosage strengths is expected. Thus, testing of three batches (each strength) at only the initial, 24 months, and proposed shelf life timepoint of 36 months is performed for samples stored under the long term storage condition.

Elevated temperature stress stability studies have been conducted on one batch each for the lowest and the highest dosage strength of dabigatran etexilate pellets, 20 mg and 150 mg/sachet. The samples were stored in the primary packaging material (without the secondary packaging). Photo stability and humidity stress studies using the 150 mg/sachet batch were performed in open containers.

(b) (4)

The dabigatran etexilate pellets have been evaluated in a food compatibility study. The results have demonstrated suitable compatibility at room temperature for a maximum period of 30 minutes. It should be noted that the previous studies assessed the compatibility over a period of 30 minutes. A new study will be performed where the duration of the compatibility assessment will be extended from 30 min to 2 hours according to FDA guidance, "Use of Liquids and/or Soft Foods as Vehicles for Drug Administration: General Considerations for Selection and In Vitro Methods for Product Quality Assessment." The new study will be performed with one primary stability batch from long term storage conditions at the 24 months timepoint and again at the end of

shelf life (36 months) and the 24 months data will be provided (b) (4) *section 3.2.P.2). Additionally, summaries of the methods and method validations will be provided in section 3.2.P.2, accordingly.*

A stability overview for the dabigatran etexilate pellets is provided in Table 2 below.

Table 2 Stability overview for dabigatran etexilate pellets

	Type of stability study	*Storage condition and Packaging*	*Maximum storage period*
Pellets	*Stress stability:* *- Temperature* *one primary stability batch of 20 and 150 mg/sachet*	*60°C (sachets only)*	*28 days*
	- Humidity *- Photostability* *One 150 mg primary stability batch*	*30°C/75 % r.h.* *Light stress conditions (ICH Q1B)* *open storage*	*24 hours* *22 hours* *(≥ 1.2 x 10^6 lux h)*
	Primary stability *3 batches each of 20, 30, 40 mg, and 150 mg with full testing;*	*25°C/60% r.h.* *Sachets in secondary protective aluminum bag with desiccant*	*24 months*
	3 batches each of 50 and 100 mg tested at long term conditions at T=0, 24, [36] months	*40°C/75% r.h.* *Sachets in secondary protective aluminum bag with desiccant*	*6 months*
	(b) (4)		
	Food compatibility study (3.2.P.2) *One primary stability batch after storage for 24 and [36] months (strength independent)*	*Pellets in soft food/apple juice* *Room temperature*	*2 hours*

Does FDA have any comments on the proposed stability data package for the dabigatran etexilate pellets formulation?

FDA Response to Question 11: The proposed stability package described for dabigatran etexilate pellets in Question 11 of the meeting package appears reasonable.

Question 12: (b) (4)

(b) (4)

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Additional Comments:

(b) (4)

3.0 OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), 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 indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

[6] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

TANYA M WROBLEWSKI
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