Boehringer Ingelheim

Non-interventional Study Protocol

Document Number:	**c17261390-03**
BI Study Number:	1321-0023
BI Investigational Product(s):	Praxbind™
Title:	Post marketing surveillance program of Praxbind™ use in India.
Brief lay title	Praxbind™ India PMS program
Protocol version identifier:	2.0
Date of last version of protocol:	12 Jul 2017
PASS:	Yes
EU PAS register number:	(The study has not been registered yet)
Active substance:	Idarucizumab
Medicinal product:	1 vial of 50 ml contains 2.5 g Idarucizumab (50 mg/ml); Total recommended dose of 5g.
Product reference:	Not Applicable
Procedure number:	Not Applicable
Marketing authorisation holder(s):	Boehringer-Ingelheim India Pvt Ltd
Joint PASS:	No
Research question and objectives:	The main objective of the Praxbind™ administration surveillance program is to evaluate the prescription patterns of use of Praxbind™ in a clinical practice setting, with special focus on ADRs and fatal AEs.

Country(-ies) of study:	India
Author:	Sumedh Bondal
Marketing authorisation holder(s):	Boehringer-Ingelheim India Pvt Ltd, 1102, 11th Floor, Hallmark Business Plaza, Gurunanak Hospital Road, Bandra East, Mumbai-400051, Maharashtra, India
In case of PASS, add: **MAH contact person:**	*Dr. Sonesh Kalra*
In case of PASS, add: **<EU-QPPV:>**	***Dr Sabine Jeck-Thole***
In case of PASS, add: **<Signature of EU-QPPV:>**	*Signature of EU-QPPV is added at the end of the Protocol in the signature page.*
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3. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorisation Holder Activities
NIS	Non-Interventional Study
SAE	Serious Adverse Event

4. RESPONSIBLE PARTIES

Boehringer-Ingelheim India Pvt Ltd,
1102, 11th Floor, Hallmark Business Plaza,
Gurunanak Hospital Road,
Bandra East, Mumbai-400051,
Maharashtra, India

Contact details and the list of all investigators will be kept in a stand-alone document.

5. ABSTRACT

Name of company: Boehringer Ingelheim India Pvt Ltd			
Name of finished medicinal product: Praxbind™			
Name of active ingredient: Idarucizumab			
Protocol date: 12 Jul 2017	**Study number:** 1321-0023	**Version/Revision:** 2.0	**Version/Revision date:** 13 Sep 2017
Title of study:	Post marketing surveillance program of Praxbind™ use in India.		
Rationale and background:	Praxbind™ (Idarucizumab) is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran with very high affinity. Praxbind™ potently and specifically binds to dabigatran and its metabolites and neutralises its anticoagulant effect. Praxbind™ is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran etexilate when rapid reversal of the anticoagulant effects of dabigatran is required: • for emergency surgery/urgent procedures OR • in life-threatening or uncontrolled bleeding. The aim of this Praxbind™ drug administration surveillance program is to collect data on Praxbind™ prescription patterns in a clinical practice setting in India.		
Research question and objectives:	The main objective of the Praxbind™ drug administration surveillance program is to evaluate the prescription patterns of use of Praxbind™ in a clinical practice setting, with special focus on ADRs and fatal AEs.		
Study design:	This drug administration surveillance program is designed as an Indian multi-centre program enrolling patients administered with Praxbind™ after launch. There are no protocol mandated follow-up visits or procedures associated with the program. No interference with usual medical care is involved, and thus it will not affect the treatment of patients. The program will apply to all participating centres where the Praxbind™ is prescribed depending on market country regulations and requirements.		

Name of company: Boehringer Ingelheim India Pvt Ltd			
Name of finished medicinal product: Praxbind™			
Name of active ingredient: Idarucizumab			
Protocol date: 12 Jul 2017	**Study number:** 1321-0023	**Version/Revision:** 2.0	**Version/Revision date:** 13 Sep 2017
	Praxbind™ is prescribed depending on market country regulations and requirements.		
Population:	Hospital (sites) with access to Praxbind™ will receive information material about the drug administration surveillance program. The target population will be all patients, who receive Praxbind™ as prescribed by the treating physician. This program will be initiated after the commercial availability of Praxbind™ in India. It will include up to 25 patients who require Praxbind™as prescribed according to the approved Indian label or the patients included in 2 years at selected centres approved by the regulatory authority, whichever is earlier. The patients who participate in 1160.189 and 1160.248 study and have a requirement for Praxbind™ will be part of this protocol. Inclusion criteria: 1. Patients treated with Pradaxa (dabigatran etexilate) capsules with requirement of rapid reversal of the anticoagulant effects of dabigatran: • For emergency surgery/urgent procedures (or) • In life-threatening or uncontrolled bleeding 2. Written informed consent in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines and local legislation and/or regulations. Exclusion criteria: • Participation in an Praxbind™ clinical trial		

Name of company: Boehringer Ingelheim India Pvt Ltd			
Name of finished medicinal product: Praxbind™			
Name of active ingredient: Idarucizumab			
Protocol date: 12 Jul 2017	**Study number:** 1321-0023	**Version/Revision:** 2.0	**Version/Revision date:** 13 Sep 2017
Variables:	Information on basic patient characteristics and use of Praxbind™ will be entered into the Praxbind™ drug administration record. The following anonymised data will be collected from the Praxbind™ administration records upon availability: 1. Site characteristics • Multi-specialty hospitals with emergency management facilities and having access to Praxbind™. • Practice type (academic, non-academic, private, Government); • Availability of prescription/medical records at the site. 2. Patient data • Year of birth • Gender: Male or Female • Vital Signs • Physical Examination • Laboratory data • Pregnancy status in case of female patient 3. Medical History • Name, dose and last intake of previous anticoagulant medications (Dabigatran); • Pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. renal impairment, congenital or acquired coagulation disorders, thrombocytopenia or functional		

Name of company: Boehringer Ingelheim India Pvt Ltd			
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Platelet defects, recent biopsy, recent surgery, major trauma, bacterial endocarditis, esophagitis, gastritis, gastroesophageal reflux, hepatic disorders, vascular disorders, neoplasms/cancer, inherited vascular disorder (aneurysms, arteriovenous malformation, microangiopathy) and the HAS-BLED score).

- Concomitant treatment pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs, clopidogrel, selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, sStrong P-Gp inhibitors (e.g. ketoconazole, clarithromycin, ticagrelor), chemotherapy, radiation therapy.

3. Praxbind™ utilization

- Department (emergency, operating room, ICU, other patient setting);
- Type of surgery / procedure if applicable;
- Information on bleeding event (pre and post Praxbind™ administration) including location (Gastrointestinal tract; Intracranial; Skin, Urogenital tract, Intramuscular, Retroperitoneal, Undefined location, Other defined location) if applicable, and if bleeding was life threatening (yes/no);
- Indication: life-threatening or uncontrolled bleeding requiring urgent medical intervention, emergency surgery or other urgent medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure, scheduled or planned surgery/procedure,

Name of company: Boehringer Ingelheim India Pvt Ltd			
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Protocol date: 12 Jul 2017	**Study number:** 1321-0023	**Version/Revision:** 2.0	**Version/Revision date:** 13 Sep 2017
	• Dosage and administration (total dose administered and time interval between the administration of the two vials; vials to be taken one after the other, immediate administration of the second vial is mandatory). • Premature Praxbind™ administration discontinuation (yes/no). • In case if the patient requires an additional 5 g dose for the following conditions as per the label: • recurrence of clinically relevant bleeding together with prolonged clotting times, or • if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or • patients require a second emergency surgery/urgent procedure and have prolonged clotting times. • Information on restart of anticoagulation therapy (which anticoagulation treatment including dose and when was it restarted). • All adverse drug reactions (ADRs, serious and non-serious) associated with Praxbind™, • All AEs with fatal outcome in patients exposed to Praxbind™		

Name of company: Boehringer Ingelheim India Pvt Ltd			
Name of finished medicinal product: Praxbind™			
Name of active ingredient: Idarucizumab			
Protocol date: 12 Jul 2017	**Study number:** 1321-0023	**Version/Revision:** 2.0	**Version/Revision date:** 13 Sep 2017
Outcomes	**Primary Outcome:-** Any suspected ADRs and fatal AEs; with special focus on hypersensitivity and thrombotic event, occurred within 7 days after Praxbind™ administration. **Secondary Outcome:-** Percentage of patients who either received Praxbind™ for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding at the end of 2 years.		
Data sources:	Data collected will be entered by the site using electronic CRF forms. It is the doctor's responsibility to ensure the accuracy of the data provided to the program by any site staff that is trained for the program data collection.		
Study size:	This program will be initiated after the commercial availability of Praxbind™ in India. It will include up to 25 consecutive patients who may require Praxbind™ prescribed according to the approved Indian label or the patients included in 2 years at selected centres approved by the regulatory authority, whichever is earlier.		
Data analysis:	A detailed analysis plan will be prepared prior to First Patient In. All variables will be presented using descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, quartiles, minimum and maximum values, 95% CIs) as appropriate for the nature of the variables (i.e. categorical or continuous).		
Milestones:	Start of data collection: Currently planned for Q4 2017 (Depending on start time of commercial availability). End of data collection: Currently planned for Q4 2019 (Depending on start of market authorisation and Praxbind™ usage). Final report: Currently planned for Q1 2020 (Depending on start of market authorisation and Praxbind™ usage).		

6. AMENDMENTS AND UPDATES

The following additions have been made to the Protocol based on the recommendations of the Drug Controller General India, DCG(I):-

Sr. No	Section	Page no.	Protocol V 2.0 dated 13 Sep 2017
1	Title Page; Abstract and Section 9:-Research question and objectives	1, 7 and 17	The main objective of the Praxbind® administration surveillance program is to evaluate the prescription patterns of use of Praxbind® in a clinical practice setting, **with special focus on ADRs and fatal AEs.**
2	Abstract:-Outcomes; Section 10.2.2.1:-Primary Outcomes	12 and 21	**Any suspected ADRs and fatal AEs; with special focus on hypersensitivity and thrombotic event, occurred within 7 days after Praxbind® administration.**
3	Abstract:-Outcomes; Section 10.2.2.2:-Secondary Outcomes	12 and 21	**Percentage of patients who either received Praxbind® for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding at the end of 2 years.**

Following administrative and typographical corrections were performed throughout the document:-

Sr No	Section	Page no.	Protocol V 2.0 dated 13 Sep 2017
1	Medicinal Product	1	**1 vial of 50 ml contains** 2.5 g Idarucizumab (50 mg/ml); **Total recommended dose of 5g.**
2	Section 7:- Milestones	18	Updated as per the new planned dates
3	Abstract:- Population; Section:-10.1.2 Study population	8, 18	The target population will be all patients, **who receive Praxbind® as prescribed by the treating physician.** It will include up to 25 ~~consecutive~~ patients who require Praxbind® **as prescribed according to the approved Indian label** or the patients included in 2 years at selected centres approved by the regulatory authority, whichever is earlier.
4	Abstract:-Variables; Section 10.2:-Variables	9, 19	Availability of prescription/medical records at the ~~pharmacy~~ **site**.

5	Abstract:-Variables; Section 10.2:-Variables	9, 19	• **Pregnancy status in case of female patient.**
6	Abstract:-Variables; Section 10.2:-Variables	11, 20	• **All adverse drug reactions (ADRs, serious and non-serious) associated with Praxbind™,** • **All AEs with fatal outcome in patients exposed to Praxbind™**
7	Section 10.1 Study Design	18	**This is a post marketing surveillance study wherein patients will be eligible for the study if they are prescribed Praxbind® as per the approved label.** The drug administration surveillance program is designed as a multi-center program enrolling patients administered with Praxbind®.
8	10.1.2 Study population	18	The target population will be all patients, who receive Praxbind® **prescribed as per the approved label.**
9	10.1.3 Study discontinuation	19	The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination ~~(except in case of the third reason)~~.
10	10.9.2. Study Records	22	Case Report Forms (CRFs) for individual patients will be provided by the sponsor **electronically**.
11	10.7 Quality Control	22	It is the responsibility of the ~~pharmacist~~ **Investigator** to ensure that the data are as accurate and complete as possible. The ~~Pharmacist~~ **Investigator** and delegate will be trained on data entry.
12	12.1. Definition of adverse events	26	~~Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.~~

- Name of study drug changed from Idarucizumab to Praxbind™ across the entire Protocol.

7. MILESTONES

Milestone	Planned Date
Final Protocol	13 Sep 2017 (Revision)
Start of data collection	15 Dec 2017
End of data collection	15 Dec 2019
Final report of study results:	30 Feb 2020

8. RATIONALE AND BACKGROUND

A clinical development program is ongoing to support marketing authorisation submissions for Praxbind™ indicated in patients treated with dabigatran who require emergency surgery/urgent procedures or who have a life-threatening or uncontrolled bleeding when rapid reversal of the anticoagulant effects of dabigatran is required.

The aim of this drug administration surveillance program is to capture a large proportion of the patients treated with Praxbind™ in order to collect data on Praxbind™ prescription patterns in a clinical practice setting in India.

Praxbind™ (Idarucizumab) is a humanized monoclonal antibody fragment (Fab) that binds to Dabigatran with very high affinity. Praxbind™ potently and specifically binds to dabigatran and its metabolites and neutralises its anticoagulant effect. Praxbind™ is a specific reversal agent for dabigatran and is indicated in patients treated with dabigatran etexilate when rapid reversal of the anticoagulant effects of dabigatran is required:

- for emergency surgery/urgent procedures
  (or)
- in life-threatening or uncontrolled bleeding

Dabigatran etexilate (Pradaxa) is an oral pro-drug of dabigatran, a direct-acting thrombin inhibitor that has been shown to be effective in the prevention or reduction of thrombotic events in:

- patients with non-valvular atrial fibrillation
- patients with deep vein thrombosis or pulmonary embolism who have been treated with a parenteral anticoagulant for 5-10 days
- patients who have previously received anticoagulant therapy for treatment of venous thromboembolism
- in orthopedic surgery patients at risk for post-operative DVT

Anticoagulation therapy is a mainstay of treatment and prevention of pathologic thrombosis in these different clinical settings. However, as with all anticoagulants, bleeding is a potential side effect. The risk of bleeding in dabigatran-treated patients during emergency surgery or other urgent invasive procedures is also a consideration.

9. RESEARCH QUESTION AND OBJECTIVES

The main objective of the Praxbind™ drug administration surveillance program is to evaluate the prescription patterns of use of Praxbind™ in a clinical practice setting, with special focus on ADRs and fatal AEs.

10. RESEARCH METHODS

This program will be initiated after the commercial availability of Praxbind™ in India. It will include patients administered with Praxbind™ into the surveillance program after commercial availability in 2 years at selected centres approved by the regulatory authority.

10.1 STUDY DESIGN

This is a post marketing surveillance study wherein patients will be eligible for the study if they are prescribed Praxbind™ as per the approved label. The drug administration surveillance program is designed as a multi-center program enrolling patients administered with Praxbind™. Data will be collected for patients who have been treated with Praxbind™ within 2 years. There are no protocol mandated follow-up visits or procedures associated with the program. No interference with usual medical care is involved, and thus it will not affect the treatment of patients.

10.1.1 Study sites

The program will be available to select hospitals approved by Indian regulatory authority with access to Praxbind™.
Hospital (sites) having access to Praxbind™ will receive information material about Praxbind™ administration surveillance program.

10.1.2 Study population

The target population will be all patients, who receive Praxbind™ prescribed as per the approved label.

The patients who participate in 1160.189 and 1160.248 study and have a requirement for Praxbind™ will be part of this protocol.

Inclusion criteria:

1. Patients treated with Pradaxa (dabigatran etexilate) capsules with requirement of rapid reversal of the anticoagulant effects of dabigatran:

- For emergency surgery/urgent procedures
  (or)
- In life-threatening or uncontrolled bleeding

2. Written informed consent in accordance with International Conference on Harmonization Good Clinical Practice (GCP) guidelines and local legislation and/or regulations.

Exclusion criteria:

- Participation in a Praxbind™ clinical trial.

10.1.3 Study discontinuation

A log of all patients included into the drug surveillance study will be maintained at the Investigational sites.

Boehringer Ingelheim reserves the right to discontinue the study overall or at a particular study site at any time for the following reasons:

1. Emergence of any efficacy/safety information of Praxbind™ that could significantly affect continuation of the study.

2. Violation of the study protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study

The investigator / the study site will be reimbursed for reasonable expenses incurred in case of study termination.

10.2 VARIABLES

1. Site characteristics:

To evaluate the diversity of sites the following information will be collected for each participating site:

- Multi-specialty hospitals with emergency management facilities and having access to Praxbind™
- Practice type (academic, non-academic, private, Government)
- Availability of prescription/medical records at the site.

Patient characteristics and Praxbind™ use:-

The following anonymised data will be collected from the Praxbind™ administration records upon availability:

2. Patient Data:

- Year of Birth
- Gender: Male or Female
- Vital Signs
- Physical Examination
- Laboratory data (Data would be collected of lab results performed as a routine practice. No additional lab tests should be performed specifically for this study purpose)
- Pregnancy status in case of female patient

3. Medical History:

- Name, dose and last intake of previous anticoagulant medications (Dabigatran);

- Pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. renal impairment, congenital or acquired coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, recent surgery, major trauma, bacterial endocarditis, esophagitis, gastritis, gastroesophageal reflux, hepatic disorders, vascular disorders, neoplasms/cancer, inherited vascular disorder (aneurysms, arteriovenous malformation, microangiopathy) and the HAS-BLED score).
- Concomitant treatment pertaining to haemorrhagic risk factors or impact on safety outcomes (e.g. acetylsalicylic acid, non-steroidal anti-inflammatory drugs, clopidogrel, selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, Strong P-Gp inhibitors (e.g. kKetoconazol, cClarithromycin, ticagrelor), chemotherapy, radiation therapy.

4. Praxbind™ utilization:

- Department (emergency, operating room, ICU, other patient setting);
- Type of surgery /procedure if applicable;
- Information on bleeding event including location (Gastrointestinal tract; Intracranial; Skin, Urogenital tract, Intramuscular, Retroperitoneal, Undefined location, Other (defined location) if applicable, and if bleeding was life-threatening (yes/no);
- Indication: life-threatening or uncontrolled bleeding requiring urgent medical intervention, emergency surgery or other urgent medical procedure necessitating rapid reversal of the anticoagulant effect of dabigatran prior to surgery/procedure, scheduled or planned surgery/procedure, other;
- Dosage and administration (total dose administered and time interval between the administration of the two vials; vials to be taken one after the other, immediate administration of the second vial is mandatory);
- Premature Praxbind™ administration discontinuation (yes/no).
- In case if the patient requires an additional 5 g dose for the following conditions as per the label:
  i. recurrence of clinically relevant bleeding together with prolonged clotting times, or
  ii. if potential re-bleeding would be life-threatening and prolonged clotting times are observed, or
  iii. patients require a second emergency surgery/urgent procedure and have prolonged clotting times.
- Information on restart of anticoagulation therapy (which anticoagulation treatment including dose and when was it restarted).
- All adverse drug reactions (ADRs, serious and non-serious) associated with Praxbind™.
- All AEs with fatal outcome in patients exposed to Praxbind™.

10.2.1 Exposures

Not Applicable

10.2.2 Outcomes

10.2.2.1 Primary outcomes

Any suspected ADRs and fatal AEs; with special focus on hypersensitivity and thrombotic event, occurred within 7 days after Praxbind™ administration.

10.2.2.2 Secondary outcomes

Percentage of patients who either received Praxbind™ for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding at the end of 2 years.

10.2.2.3 Further outcomes

Not Applicable

10.2.3 Covariates

Not Applicable

10.3 DATA SOURCES

Data collected from patient's medical notes and hospital records will be entered by the site directly in the paper based forms. All sites will be fully trained for using the CRF forms. It is the site's responsibility to ensure the accuracy of the data provided to the program by any site staff that is trained for the program data collection. The program does not entail any change in prescribing pattern or management policies which are left to the discretion of the treating physician. No special evaluation procedure is required. The data to be entered in the e-CRFs is part of the information that should be generally available during routine medical practice.

Data will be transferred to the Sponsor after closure of the program.

10.4 STUDY SIZE

This program will be initiated after the commercial availability of Praxbind™ in India. It will include up to 25 patients who require Praxbind™ according to the approved Indian label or the patients included in 2 years at selected centres approved by the regulatory authority, whichever is earlier.

10.5 DATA MANAGEMENT

A data management plan will be created before data collection begins and will describe all functions, processes, and specifications for data collection and validation.

10.6 DATA ANALYSIS

10.6.1 Main analysis

A detailed analysis plan will be prepared prior to First Patient In.

All variables will be presented using descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, quartiles, minimum and maximum values, 95% CIs) as appropriate for the nature of the variables (i.e. categorical or continuous).

10.6.2 Further analysis

Not Applicable.

10.7 QUALITY CONTROL

It is the responsibility of the Investigator to ensure that the data are as accurate and complete as possible. The Investigator and delegate will be trained on data entry.

Data will be recorded by local site staff directly into the e-CRF's. Data quality will be ensured by implementation of validations and edit checks.

No patient identifying information will be available to non-study staff except Ethics Committee and regulatory agencies during inspections.

10.8 LIMITATIONS OF THE RESEARCH METHODS

This study will include only up to 25 consecutive patients who require Praxbind™. The data analysis will be done using descriptive statistics with no formal statistical hypothesis.

10.9 OTHER ASPECTS

10.9.1 Data quality assurance

A quality assurance audit/inspection of this study may be conducted by the sponsor or sponsor's designees or by Institutional Review Board (IRBs) / Independent Ethics Committee (IECs) or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation of this study.

10.9.2 Study records

Case Report Forms (CRFs) for individual patients will be provided by the sponsor electronically.

10.9.2.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the e-CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For e-CRFs, the following data need to be derived from source documents:

- Patient identification (gender, date of birth)
- Patient participation in the study (product, study number, patient number, date patient was informed)
- Dates of Patient's visit, (including Praxbind™ administration & Hospital Admission details)
- Medical history (including indication and concomitant diseases, if applicable)
- Medication history
- Adverse events (onset date (mandatory), and end date (if available))
- Serious adverse events (SAEs) (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Laboratory results
- Conclusion of Patient's Participation in the study

10.9.2.2 Direct access to source data and documents

The Investigator / institution will permit active surveillance study related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents.

e-CRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review.

The Clinical Research Associate (CRA)/ on site monitor and auditor may review all e-CRF and written informed consents.

10.9.2.2.1 Storage of records

Site(s)

The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor

The sponsor must retain the essential documents according to the sponsor's SOPs.

11. PROTECTION OF HUMAN SUBJECTS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (to the extent applicable to the NIS setting and required by local regulations), Good Epidemiological Practice (GEP), Guidelines for Good Pharmacoepidemiology Practice (GPP), and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalization of the Study Report.

11.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

In addition to review and approval by Drug controller general of India (DCGI), the approval of Institutional Review Board (IRB) or Ethics Committee will be sought as per the institutional procedures before the start of this active surveillance.

Prior to patient participation in this active surveillance study, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to the regulatory and legal requirements of India. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The Investigator must give a full explanation to the participants of this active surveillance regarding the collection of the safety data at specific time points. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign and date the informed consent form.

The patient must be informed that his/her personal study-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorized monitors (CML/CRA) or Quality Medicine auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

11.2 STATEMENT OF CONFIDENTIALITY

Upon Praxbind™ administration, anonymized patient data will be collected. Every site participating in the surveillance program should collect the patient data anonymously. No data will be key-coded to the patient's identity.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

12.1 DEFINITIONS OF ADVERSE EVENTS

Adverse event
An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event
A serious adverse event is defined as any AE which
- results in death,
- is life-threatening,
- requires in-patient hospitalization, or
- prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Adverse Event of Special Interest (AESI)
The term Adverse Event of Special Interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring

and safety assessment within this study, e.g. the potential for AEs based on knowledge from other compounds in the same class.

No AESIs have been defined for this study.

12.2 ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

The investigator shall maintain and keep detailed records of all AEs in their patient files.

Collection of AEs
The study design is of non-interventional nature and the study is conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the studied BI drug. For this reason the following AE collection and reporting requirements have been defined.

The following must be collected by the investigator in the (e) CRF from signing the informed consent onwards until the end of the study:

- all adverse drug reactions (ADRs, serious and non-serious) associated with Praxbind™,
- all AEs with fatal outcome in patients exposed to Praxbind™.

All ADRs , including those persisting after study completion must be followed up until they are resolved, have been sufficiently characterized, or no further information can be obtained.

The investigator carefully assesses whether an AE constitutes an ADR using the information below.

Causal relationship of adverse event
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest **a reasonable causal relationship** could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**.
- A **plausible time to onset of the event** relative to the time of drug exposure.
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g. preexisting or concomitant diseases, or co-medications).

- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

Arguments that may suggest that there is **no reasonable possibility of a causal relationship** could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remains unchanged.

Intensity of adverse event

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) which is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria in the (e) CRF.

Pregnancy:

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken Praxbind™, the investigator must report any drug exposure during pregnancy, which occurred in a female subject or in a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed, otherwise the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited Reporting of AEs and Drug Exposure During Pregnancy

BI
BI Contacts for AE/ Pregnancy Reporting: Phone: +91-22-26456477/78 *Fax Number: +91-22-26456163* Email ID: PV_local_India@boehringer-ingelheim.com

The following must be reported by the investigator on the NIS AE form from signing the informed consent onwards until the end of the study:

Type of Report	Timeline
All **serious ADRs** associated with Praxbind™	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to Praxbind™	immediately within 24 hours
All **non-serious ADRs** associated with Praxbind™	7 calendar days
All **pregnancy monitoring** forms	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the NIS AE form.

Information required

For each reportable adverse event, the investigator should provide the information requested on the appropriate (e)CRF pages and the NIS AE form.

Reporting of the indication for which Praxbind™ is used

For patients not participating in 1160.189 or 1160.248, the investigator must report the indication for which Praxbind™ is used (emergency surgery/urgent procedures or life-threatening or uncontrolled bleeding) as spontaneous Pradaxa (dabigatran etexilate) case to the above mentioned BI contact for AE/Pregnancy Reporting.
For emergency surgery/urgent procedures the underlying condition requiring the surgery/procedure must be indicated in the report.

This reporting obligation is independent of causality assessment, but a causality assessment must always be provided.

For patients participating in 1160.189 or 1160.248, the reporting of the indication for which Praxbind™ is used must occur within those trials following the requirements for 1160.189 or 1160.248 respectively.

Reporting of related Adverse Events associated with any other BI drug

The investigator is encouraged to report all adverse events related to any BI drug other than Praxbind™ according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred or not, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and unexpected benefit.

(If the event associated to the indication for Praxbind™ is considered related to Pradaxa (dabigatran etexilate), see section "Reporting of the indication for which Praxbind™ is used").

12.3 REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies will be done by the MAH according to local and international regulatory requirements.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigator and of the sponsor with regard to publication of the results of this study are described in the investigator contract. As a general rule, no study results should be published prior to finalisation of the Study Report.

14. REFERENCES

14.1 PUBLISHED REFERENCES

None

14.2 UNPUBLISHED REFERENCES

None

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Post marketing surveillance program of Praxbind™ use in India.

Study reference number:
1321-0023

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	7
1.1.2 End of data collection[2]	☒	☐	☐	7
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	Pg. no. 1
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

1.1.5 EU PAS Registration will be completed after the Protocol is finalized.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	8
2.1.2 The objective(s) of the study?	☒	☐	☐	9
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	10.1.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.4.- No formal hypothesis is being tested in the PMS study
2.1.5.- No formal hypothesis is being tested in the PMS study

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	10.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	10.2.2

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	10.6.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	12

Comments:

3.3.- This is not applicable in case of a NIS study on Praxbind™ with no defined incidence rate for this study.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	10.1.2
4.2 Is the planned study population defined in terms of:	☐	☐	☒	
4.2.1 Study time period?	☒	☐	☐	10.2
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	10.2
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Duration of follow-up?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	10.1.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	10.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Praxbind™ is administered as a total dose (5g) across two separate vials of 2.5g each one after the other immediately.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	10.2.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	10.2.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☒	☐	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☒	☐	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☐	☒	☐	
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	
7.3 Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

Since there is no comparator arm in the study and only one standard dose of study drug is studied, there are no confounding variables. Hence, the entire section is not applicable.

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

This is an India only study and hence there will be no sub-group analysis done for this study.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	10.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	10.3
9.1.3 Covariates?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	10.2.1
8.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	10.2.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	10.2.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

9.3.- The coding system will be a part of the Data Analysis plan.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	10.6.1
10.2 Are descriptive analyses included?	☒	☐	☐	10.6.1
10.3 Are stratified analyses included?	☐	☐	☒	
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	10.4

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10.9.2.2.1
11.2 Are methods of quality assurance described?	☒	☐	☐	10.9.1
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	10.9
12.1.2 Information bias?	☒	☐	☐	10.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	10.4

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	11.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	11.1
13.3 Have data protection requirements been described?	☒	☐	☐	11.1

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	6

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable

APPROVAL / SIGNATURE PAGE

Document Number: c17261390 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol-version-02

Title: Post marketing surveillance program of PraxbindTM use in India.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	Bondal,Sumedh	14 Sep 2017 16:56 CEST
Approval-EU Qualified Person Pharmacovigilance	Jeck-Thole,Dr.,Sabine	15 Sep 2017 08:46 CEST
Approval-Pharmacovigilance	Lohrmann,Dr.,Emanuel	15 Sep 2017 11:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed