Boehringer Ingelheim

Redacted Protocol

Protocol: Evaluation of potential off-label use of dabigatran etexilate in Europe

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BI Study No.:	1160.144
Product(s):	Dabigatran etexilate
Title:	Evaluation of potential off-label use of dabigatran etexilate in Europe (Brief Common Protocol)
Team Member Epidemiology:	[redacted]
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Study Sponsor:	Boehringer Ingelheim
Planned Dates of Study:	1Q 2014 to 1Q 2016

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OBSERVATIONAL STUDY PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim GmbH		
Name of product: **Pradaxa**		
Name of active ingredient: **Dabigatran etexilate**		

Protocol date	**Study number**	**Planned study period**
8 March 2012 (Revised 19 May 2014, V4)	1160.144	1Q 2014 to 1Q 2016

Title of study:	Evaluation of potential off-label use of dabigatran etexilate in Europe (Brief Common Protocol)
Team Member Epidemiology:	[redacted]
Project Team:	RTI Health Solutions: Cristina Varas-Lorenzo (project director), Manel Pladevall, Susanne Perez-Gutthann Boehringer Ingelheim: [redacted]
Study data source:	Proposed population-based data sources are the following: the Clinical Practice Research Datalink (CPRD), United Kingdom (UK); National Databases, Denmark; and Cegedim, France.
Objectives:	• To estimate the proportion of off-label use in new users of dabigatran etexilate according to the electronically recorded clinical indication or generated proxies for indication as available in each database. • To describe the characteristics of new users of dabigatran etexilate, including dose, demographics, clinical indication, morbidity, and use of other medications prior to the first captured prescription, stratified by usage sub-group—on- or off-label use.

Methodology/Study design:	Descriptive, observational, multi-country European cross-sectional study of new users of dabigatran etexilate that will characterise on- and off-label use status and other medical characteristics at the time of the first prescription. *The study population* will include new users of dabigatran etexilate in the study period. *New users* will be defined as those patients who initiate treatment with dabigatran etexilate during the study period and who have not used it during the previous year. The *index date* will be defined as the date on which each identified new user receives the first prescription (*index prescription*) for dabigatran etexilate. The *study period* will encompass the time period from the launch of dabigatran etexilate for the prevention of stroke in atrial fibrillation in each country until the target number of new users is reached in each selected country-specific database. The study period and its length could therefore be different for each country-specific study.
Expected number of patients:	The study size will be driven by the uptake of dabigatran etexilate following the approval and launch of the new indication for the prevention of stroke in atrial fibrillation in the populations from which the automated databases obtain data. The estimated study size for each country-specific database is approximately 5,000 new users of dabigatran etexilate.
Main criteria for inclusion:	Patients who received a new prescription of dabigatran etexilate will be required to meet the following criteria, as ascertained from each of the selected automated databases: • Have at least 1 year of enrolment in the electronic database. • Have not been prescribed dabigatran etexilate during the 1-year period prior to the index date. A minimum period of 1 year prior to the index date is considered the *baseline period*.
Main criteria for exclusion:	No age restrictions or exclusion criteria will be applied, but age and sex information should be available.
Study product:	Dabigatran etexilate (ATC: B01AE07)
Comparison group:	None
Expected duration of exposure:	Not applicable

Outcomes:	The main outcome of this study is the proportion of off-label use estimated among new users of dabigatran etexilate; new users will be characterised. The definition of off-label use of oral dabigatran etexilate outside atrial fibrillation will be based on use for a disease or medical condition other than the labelled indications. For Pradaxa, the full approved indications by the European Medicines Agency are as follows: • Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery • Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors: – Previous stroke, transient ischaemic attack, or systemic embolism – Left ventricular ejection fraction < 40% – Symptomatic heart failure, New York Heart Association (NYHA) Class 2 or higher – Age ≥ 75 years – Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension A revision of this indication statement was submitted for approval in the European Union (EU) in September 2013. The revision became effective in December 2013, introducing the following modified indication statement: "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension." Indication for treatment will be assessed according to data available in each selected database, taking into account the approved indication at different time periods (i.e., the indication statement approved at the time of the index date). Indication will be further assessed in random samples of users (n = 200) through the manual review of computerised patient profiles created from the CPRD. The patient profile is a de-identified chronological list of medical events and drug prescriptions based on the computerised database information. In the absence of labelled indications, potential off-label use could include, but is not limited to, the following:

	• General thrombosis prophylaxis other than hip and knee orthopaedic surgery • Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (CHMP opinion 25 April 2014), until Commission Decision • Anticoagulation for patients with heart valve replacement or a stent • General prophylaxis or treatment of a thrombus in any site • Hypercoagulability • Pediatric patients; because dabigatran has been approved for use only in adults, any use in the pediatric age groups will be considered off-label • In addition, the proportion of users with each contraindication, such as patients with severe renal impairment, will be described. A preliminary list of ICD-10-CM codes to identify these conditions is provided in this brief common protocol. In addition, the set of algorithms to be used as proxies for identification of potential clinical indications will be defined and described in the detailed, database-specific study protocol.
Data Analysis Methods:	All the results will be presented for each country-specific database. The analyses will be descriptive. Assessment at baseline will include data for a minimum of the 1 year before the index date (for the definition of the clinical indication) and all available data (for assessment of the prior history of diseases and clinical conditions). For components included in the definition of certain proxies for indication, all available data will also be used. With these data, the following analyses will be performed in each database study: • Age and sex distribution (includes pediatric age) • Proportion of patients with a prior diagnosis of specific diseases and clinical conditions of interest • Proportion of patients with a history of specific types of diseases prior to the index date, including contraindications (e.g., severe renal impairment) • Proportion of patients tested for renal function during the baseline period and before the first prescription of dabigatran etexilate • Proportion of patients using specific medications; use of medications will be based on the 6 months prior to the index prescription • In the Cegedim (France) database, all the information from new users of dabigatran etexilate will be described by the type of panel, primary care physicians or specialists, and according the clinical specialty, cardiologist or other, as available The main analysis will be to estimate (with 95% confidence intervals)

	the prevalence of off-label use among new users of dabigatran etexilate during the overall study period in each of the study populations. The proportion of each of the most common off-label use indications will be described among the overall off-label use group. The proportion of users in the pediatric age subgroup will be calculated. For each approved clinical indication, separately, the risk profile and use of selected drugs among new users of dabigatran etexilate will be described. The distribution of the daily prescribed dose at the index date (based on the index prescription) will be described, overall and by on-label and off-label indication sub-group. To evaluate the differences between sub-groups by indication, proportions for categorical variables and means for continuous variables will be estimated (with 95% confidence intervals) within each sub-group. A weighted, pooled prevalence of off-label use among new users of dabigatran etexilate for the entire study population (study populations of the CPRD, Cegedim, and Danish national databases combined) will be estimated (with 95% confidence intervals) when the individual results of all three databases are available.

1. BACKGROUND

Dabigatran etexilate (Pradaxa) is an oral anticoagulant approved in Europe in 2008 for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip or knee replacement surgery. In October 2010, the United States (US) Food and Drug Administration (FDA) approved dabigatran etexilate for a new indication—to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). Dabigatran etexilate has been approved for the prevention of stroke and systemic emboli in patients with non-valvular AF in Canada, Japan, Australia, and other countries. On 14 April 2011, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion for the new indication, the pertaining Commission Decision was granted on 1 August 2011.

The approved indication for Pradaxa (1 August 2011) was as follows [P11-09429]:
For 75 and 110 mg strength

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery (pVTEp).

For 110 and 150 mg strengths

Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) with one or more of the following risk factors:

- Previous stroke, transient ischaemic attack (TIA), or systemic embolism (SEE)
- Left ventricular ejection fraction < 40 %
- Symptomatic heart failure, New York Heart Association (NYHA) Class 2 or higher
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

A revision of this indication statement was submitted for approval in the European Union (EU) in September 2013. The revision became effective in December 2013, introducing the following modified indication statement: “Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension.”

The following contraindications were in the label for Pradaxa approved in the EU in August 2011:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (creatinine clearance < 30 mL/min)
- Active clinically significant bleeding
- Organic lesion at risk of bleeding
- Spontaneous or pharmacological impairment of haemostasis

- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, and tacrolimus

The contraindications have been updated since August 2011, and the following contraindication(s) are approved in the current EU label for Pradaxa:

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (creatinine clearance < 30 mL/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration; presence of malignant neoplasms at high risk of bleeding; recent brain or spinal injury; recent brain, spinal, or ophthalmic surgery; recent intracranial haemorrhage; known or suspected oesophageal varices; arteriovenous malformations; and vascular aneurysms or major intraspinal or intracerebral vascular abnormalities (contraindication extended since June 2012)
- Concomitant treatment with any other anticoagulants, e.g., unfractionated heparin (UFH), low-molecular-weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux etc.), oral anticoagulants (warfarin, rivaroxaban, apixaban, etc.), except under the circumstances of switching therapy to or from Pradaxa or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (contraindication added since June 2012)
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole, tacrolimus (tacrolimus contraindication deleted since December 2013), or dronedarone (use of dronedarone contraindicated since August 2012)
- Prosthetic heart valves requiring anticoagulant treatment (since January 2013)

As a regulatory pharmacovigilance commitment, the EMA requested Boehringer Ingelheim International GmbH (BI) to provide a study protocol for "a study to assess potential off-label use [of the medication] outside of atrial fibrillation (AF)." The study protocol was originally submitted to the EMA in August 2011, and a CHMP opinion was finally adopted October 2012. The protocol is proposed to be revised to include several label updates and revised target countries based on reimbursement and medication uptake.

Epidemiological studies on the use of drugs are essential to evaluate the intended and adverse effects of prescription medications as they are used in clinical practice. Drug use and patient characterisation studies allow for characterisation of users of the medication in terms of age and sex, treatment indication, use of concurrent medications, prior morbidity, and other characteristics. Therefore, the description of users of the medication of interest according to their clinical indication for use will allow for the evaluation of potential off-label use.

2. OBJECTIVES

- To estimate the proportion of off-label use in new users of dabigatran etexilate according to the electronically recorded clinical indication or generated proxies for indication as available in each database.
- To describe the characteristics of new users of dabigatran etexilate, including dose, demographics, clinical indication, morbidity, and use of other medications prior to the first captured prescription, stratified by usage sub-group—on- or off-label use.

3. STUDY DESIGN

This brief common protocol is for a descriptive, observational, multi-country European cross-sectional study of new users of dabigatran etexilate that will characterise on- and off-label status and other medical characteristics at the time of the first captured prescription. The common study protocol will guide the implementation of this study but for each database, a database-specific protocol based on this protocol will be developed and will include specifications adapted to each database.

3.1 POPULATION-BASED DATA SOURCES

The planned reimbursed launch of Pradaxa for the new (SPAF) indication has taken place sequentially across European countries. For this study, we are focusing on the United Kingdom (UK), reimbursement approved in August 2011; France, reimbursement approved in July 2012; and Denmark, reimbursement approved in August 2011. In all three countries, approved reimbursement for the SPAF indication is in place.

The use of dabigatran etexilate, in the approved indication for "primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery" will be initiated and concentrated mainly in the hospital but could also extend to the outpatient setting for a limited period of time after hospital discharge. The standard dosing in the summary of product characteristics recommends starting treatment within 1 to 4 hours of surgery with a half dose of 110 mg and thereafter with 220 mg once daily (taken as two capsules of 110 mg) for 10 days after knee replacement and for 28 to 35 days after hip replacement [R11-4002].

For the approved SPAF indication, dabigatran etexilate is expected to be mainly prescribed, with some potential variations across European countries, by internal medicine specialists, cardiologists, and general practitioners (GPs), but most of the follow-up prescriptions (for chronic treatment) will be issued by GPs or primary care physicians. As the study implementation progresses through time, if new indications are approved for the use of dabigatran etexilate, new changes in the label will be taken into account for the characterisation of off-label use and contraindications.

This drug utilisation study, focused on describing the potential off-label use of dabigatran etexilate, will be conducted in automated health care databases in which information on prescriptions and disease occurrence (e.g., outpatient diagnoses, hospitalisations) is recorded

on an ongoing basis. Because most of the prescriptions of interest will be chronic and therefore expected to be captured in primary health care databases, the data sources will include the Clinical Practice Research Datalink (CPRD) in the UK, the French Cegedim Strategic Data (CSD) database, and the national databases in Denmark.

3.1.1 The Clinical Practice Research Datalink, UK

The Clinical Practice Research Datalink (CPRD) (website: cprd.com/researcher/), formerly the General Practice Research Database (GPRD), contains diagnostic and prescribing information recorded by general practitioners (GPs) as part of their routine clinical practice in the United Kingdom (UK). The database covers approximately 5 million of the UK population. Patients registered are representative of the whole UK population in terms of age and sex. These data are linkable, at least partially, with other health care datasets (e.g., hospitalisation records, national mortality data) via the patient's National Health Service (NHS) number, sex, date of birth, and postal code. Updated, valid, linked CPRD data are available through the CPRD Division of the UK Medicines and Health Care Products Regulatory Agency (MHRA).

Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the database. Read codes are used for diagnoses and Multilex codes are used for medications. Additional diagnostic and treatment information can be found in free-text fields, letters from specialists and hospitals, and other sources. Identifying patients who have both CPRD and Hospital Episode Statistics (HES) data enables access to the hospitalisation data, including disease and procedural coding.

3.1.2 Cegedim Strategic Data, France

The French Cegedim Strategic Data (CSD) database (website: cegedimstrategicdata.com) includes prescription, medical history, and outpatient diagnosis information for about 2.6 million patients [R11-4003]. The database covers metropolitan France.

Usually the social security agency reimburses the prescriptions based on the clinical importance of the medication, from 15% for those medicines with low importance, 30% for medicines of moderate importance, 65% for important medicines, to 100% for medicines known to be irreplaceable and expensive [R11-4009]. To be reimbursed, the prescription must be made within the therapeutic indications on the label, and the medications must be on the list of drugs reimbursed by social security. The percentage not reimbursed might be covered by private insurance.

Repeated prescriptions can be refilled at the pharmacy without seeing the doctor. The number of allowed refills is recorded in the database. The database is not used for payment purposes, and the recorded prescriptions cover both reimbursed and unreimbursed medications. An associated diagnosis is always recorded with an issued prescription, but not necessarily the clinical indication.

The longitudinal patient database includes the following raw data:

- Demographic information (age, sex)
- Medical history (event dates, diagnoses, risk factors, referrals to specialists)
- Therapeutic history (generic and brand name, date and duration of prescription, dosage)
- Additional information (test results, immunisations, height, weight, blood pressure)

The therapeutic classification in the database has been mapped to the Anatomical Therapeutic Chemical (ATC) classification system. Signs, symptoms, diagnoses, and diagnostic tests have been mapped to the corresponding ICD-10 codes.

The Cegedim panel of participating medical doctors is selected from a large number of French physicians who use the Cegedim management software for their daily practice. These office-based, active physicians have agreed to upload to CSD servers anonymous and coded excerpts from medical files of patients who have come to see them. The data collected are gathered for each patient within the same doctor's office, thus providing longitudinal data on the same patients. The representativeness of the panel of physicians is checked using three criteria known to influence prescribing: age, sex, and geographic area of coverage. However, there are limitations in this database such as no availability of information on hospitalisations, deaths, or date transferred out of the system. Data from panels of primary care physicians and data from specialist panels are available. Panels of specialists are independent of GP panels; therefore, an overlap between patients included in primary health practices and in those from specialists could occur but it is not possible to link individual patients across the two types of practitioners. For this study, it is planned to include also information gathered by cardiologists due to the potential that the first prescription of Pradaxa will be issued by these specialists. Therefore, all the information should be stratified by the type of panel and clinical specialty. Oral anticoagulants are expected to be recorded completely when prescribed by the physicians participating in the panel; however, the first prescription can be missed if issued in the hospital or outside of the participating physicians.

3.1.3 The Danish National Databases

The Danish health care system provides universal coverage to all Danish residents, approximately 5.5 million inhabitants, including visits to GPs and specialists, hospital admissions, and outpatient visits. The costs of medicines are partially covered by the Danish health system. The centralised Civil Registration System in Denmark allows for personal identification of each Danish person and for the possibility of linkage to all Danish registries containing civil registration numbers, such as the Danish National Registry of Patients, Danish National Prescription Database, Prescription Databases of the Central Denmark Region, and the Danish Registry of Causes of Death. Data collected in these registries could be available for research purposes through collaboration with a local university or investigator affiliated with a research institute for accessing the data, if approved by the Danish National Board. The following three national registries will be of particular interest for the potential implementation of the drug utilisation study (DUS) of dabigatran etexilate:

- The Danish National Registry of Patients includes data on all hospital admissions since 1 January 1977 and on outpatient clinic and emergency department visits since 1995. Hospital discharge diagnoses and information on surgical procedures, in-hospital deaths,

and some selected drugs are recorded. After 1993, hospital discharge diagnoses are coded using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, 10th Revision* (ICD-10).

- The Danish National Prescription Database provides patient-level data on drug prescriptions dispensed by pharmacies since 1994. The National Prescription Database collects data on reimbursed and unreimbursed drugs.
- The Danish General Practice Database (DAMD) provides information from selected general practices at the national level, with the purposes of promoting and improving the quality of care in general practice and providing data for research concerning general practice. The website for the DAMD (website: dak-e.dk/flx/en/danish-general-practice-database/) reports that "Key data are transferred from the GP's electronic health record system to the database. Most data are automatically collected by the Sentinel Data Capture—these data include prescribed drugs, National Health Service disbursement codes, laboratory analysis results, and International Classification of Primary Care (ICPC) diagnoses. Additional information is collected via pop-up screens which the GP has to fill in during the consultation. The pop-up screen is designed specific for the chronic disease in question or for a particular research project. All data are linked to the patient's personal ID and the time stamp for the consultation and stored in the DAMD." Hosted at the University of Southern Denmark, the database covered approximately 1 million population in 2012, but this is increasing through time [R13-5415]. Access to almost the entire covered population is also possible for selected information.

3.2 SUMMARY OF DATA SOURCES

Table 1 summarises the main characteristics of the automated primary health databases that are proposed for study implementation. A focused feasibility evaluation has confirmed the availability of key information, lag time for data downloads, and other key parameters. Custodians of the three databases have confirmed their interest in participating in the study.

A search of the literature has identified studies on atrial fibrillation in each of the three databases. In the CPRD, a study on the incidence of atrial fibrillation based on recorded GP diagnoses confirmed the identified cases through questionnaires sent to GPs [R10-0421]. In the Danish national databases, the validity of the diagnoses of atrial fibrillation (AF) and atrial flutter (AFL) recorded in the Danish National Patient Registry has recently been reported to be high [R13-5417]. According to this review of medical records for incident cases of AF and/or AFL in the Diet, Cancer, and Health cohort study, the positive predictive value of the combined diagnosis of AF and/or AFL was 92.6% (95% confidence interval, 88.8%-95.2%), with no difference between sexes. A specified diagnosis of AFL was rarely used and was not reliable to distinguish between cases of AF and AFL. Using data from Aarhus, the risk of AF/AFL associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) has been reported [P11-08175]. Finally, an unpublished reference was found for a study on patients with atrial fibrillation performed using Cegedim, France; no details are available [R11-4018].

Table 1 Characteristics of automated primary health care databases available in the UK, Denmark, and France

Description	UK (N = 61,634.6)[1] CPRD	Denmark (N = 5,552.0) Patient and Prescription National Databases	France (N = 64,350.8)[1] Cegedim Strategic Data
Database type	Primary health care electronic medical record database plus linkage to HES and other data	National health record databases capable of linkage with other databases though the unique personal number assigned by the Central Person Registry	Primary health care electronic medical record database
Database population[2]	5.1 million	5.6 million	2.6 million
Approximate proportion of the country's population covered by the database	8%	100%	4%
Potential number of dabigatran etexilate users in 2012 captured in the database (based on BI sales estimates)	8,000	15,000	4,000
Data on medications	GP prescriptions	Pharmacy-dispensed prescriptions, reimbursed and unreimbursed.	GP prescriptions and Cardiologists prescription
Dose	Prescribed dose	Formulation strength	Prescribed dose
Duration	As indicated by the written prescription	Based on dispensed prescriptions	As indicated by the written prescription

Table 1 (cont'd) Characteristics of automated primary health care databases available in the UK, Denmark, and France

Clinical indication	Associated with new courses of medications, but completeness is variable. Computerised free-text information is available for review.	Not specifically recorded but based on proxies	Associated with new courses of medications, but completeness is variable
Outpatient diagnosis	Yes (Read codes)	Only outpatient hospital diagnosis in the patient register (ICD-10-CM); primary care diagnoses in DAMD (ICPC codes)	Yes (ICD-10-CM)
Hospital diagnosis	Recorded by GPs and partial linkage to HES (Read and ICD-10-CM)	Yes (ICD-10-CM)	No
Access to medical records	GPs, and partial linkage to HES	Partial access to hospitals, only in some regions	No
Prior atrial fibrillation assessment	Yes, based on recorded Read codes and validated through GP survey [R10-0421]	Yes (AF diagnosis with positive predictive value of 93%) [R13-5417]	Yes, based on recorded information, but unpublished [R11-4018]
Lifestyle risk factors	Yes	Yes, in DAMD	Yes
Data availability	Since 1987	Since 1994	Since 1994
Updates	At 3- to 4-month intervals	Yearly	Monthly
Approximate time lag	6-12 weeks	2012 data available in 3-4Q 2013	2-7 months

GP = general practitioner; CPRD = Clinical Practice Research Datalink; HES = Hospital Episode Statistics (database); ICPC = International Classification of Primary Care; UK = United Kingdom.

1 In thousands. Population data from EuroStat. 2009. Accessed 2 Aug 2011. Available at: Website: epp.eurostat.ec.europa.eu/portal/page/portal/product_details/publication?p_product_code=KS-QA-09-047.

2 Based on “active” patients (i.e., patients having consulted a GP at least once in the year).

3.3 STUDY POPULATION

The study population will include new users of dabigatran etexilate in the study period. *New user* will be defined as those patients who initiate treatment with dabigatran etexilate during the study period and who have not used it during the previous 1 year.

The *study period* will encompass the time period from the launch of dabigatran etexilate for the new indication in each country until the target number of new users is reached in each selected country-specific database. The study period and its length could therefore be different for each country-specific study.

3.3.1 Monitoring of dabigatran etexilate users

The first step in this study will be to monitor periodically the number of dabigatran etexilate users until the target number of new users has been reached to implement the study. The number of patients receiving prescriptions for dabigatran etexilate (irrespective of indication or dosage) will be monitored in the selected databases. The timing of the start and periodicity of the monitoring will be determined based on the lag time and update schedule for prescription data in each specific database. See Table 1.

3.3.2 Index prescription

The first captured prescription for dabigatran etexilate in the study period for each new user in the source population will be the *index prescription*. The ATC code for dabigatran etexilate is B01AE07 (see Appendix 3).

3.3.3 Index date

The *index date* will be defined as the date on which each identified new user receives the first prescription for dabigatran etexilate.

3.3.4 Inclusion criteria

Patients who received a new prescription of dabigatran etexilate will be required to meet the following criteria, as ascertained from each of the final selected automated databases:

- Have at least 1 year of enrolment in the electronic database.
- Have not been prescribed dabigatran etexilate during the 1-year period prior to the index date. A minimum of 1-year period prior to the index date is considered the "baseline period."

No age restrictions or exclusion criteria will be applied. This will allow for the characterisation of all users of dabigatran etexilate according to each potential indication for which the medication is being used, including on-label indications and potential off-label uses. This will include any pediatric population and patients with contraindications (e.g., severe renal impairment).

Specific inclusion criteria for each database might need to be applied. These criteria will be specified in the adapted protocol for each database before study implementation. As an example, in CPRD only patients with permanent registration status in "up to standard" participant general practices will be included in the study.

3.3.5 Treatment indication

The indication or reason for treatment will be assessed according to the data available in the selected databases. The indication for a new course of treatment is most often not recorded in a systematic way in existing databases, and the degree of completeness of recording this information is variable across databases. In some primary health databases like the CPRD, the indication for a prescription is usually recorded the first time a new drug is prescribed by the general practitioner (GP). Similarly, the French Cegedim systematically records a clinical diagnosis associated with specific courses of medications. However, in the Danish national databases, data on indication is based on proxies.

It is expected that a proportion of new courses of dabigatran etexilate may not have a clearly associated clinical indication. Therefore, proxies for indication will be created using computer algorithms based on sets of diagnostic, procedural, and medication codes. These algorithms will be included in the detailed, database-specific study protocol. These indication-proxy algorithms will be helpful to search a time period before or concurrent with the index date. A minimum period of 1 year prior to the index date is considered the baseline period for determination of the clinical indication. However, all available historical data on diseases and medications might be used to develop valid algorithms for some indications.

3.3.5.1 CPRD Manual Patient Profile Review

Indication will be further assessed in random samples of users through the manual review of computerised patient profiles created from the CPRD database. The patient profile is a de-identified chronological list of medical events and drug prescriptions based on the computerised database information, including free-text information if available. Review of these profiles will provide insight into medical events leading up to the prescription of a new course of medication. This information will also be used to validate the created computer algorithms to identify clinical indications. The target number will be at least 200 patient profiles. However, this number might be increased for the validation exercise if the number of sub-groups by potential clinical indication is larger than eight, to allow for a minimum review of 25 patient profiles per sub-group. Additional samples will be reviewed if the created computer algorithms need to be modified.

3.3.6 Study size

The study size will be driven primarily by the uptake of dabigatran etexilate in the populations from which the automated databases obtain data. The estimated study size for each country-specific database is approximately 5,000 new users of dabigatran etexilate. As can be seen in Table 2, a study size between 2,000 and 5,000 patients per database offers an

acceptable level of precision in the different scenarios of available number of users. However, with 5,000 patients, at the 95% level of confidence the level of precision could be adequate even when estimating the percentage of off-label use by different groups of clinical use. The final study size will depend of the uptake of the medication in each country.

Table 2 Binomial confidence intervals for different study sizes and possible percentages of off-label use

Number of patients	Lower and upper bounds of 95% confidence intervals for example off-label use percentages (%)									
	1%		2%		5%		7%		10%	
2000	0.6	1.5	1.4	2.7	4.1	6.0	5.9	8.2	8.7	11.4
3000	0.7	1.4	1.5	2.6	4.2	5.8	6.1	8.0	8.9	11.1
4000	0.7	1.4	1.6	2.5	4.3	5.7	6.2	7.8	9.1	11.0
5000	0.7	1.3	1.6	2.4	4.4	5.6	6.3	7.7	9.2	10.9

Note: Calculations were performed using Stata software.

3.4 EXPOSURES

The exposure of interest is dabigatran etexilate.

3.4.1 Dose

The distribution of the daily prescribed dose at the index date will be described for all new users of dabigatran etexilate as well as by indication sub-group (on- or off-label use). The dose described will be the one associated to the index prescription. The daily dose of medications is recorded in the CPRD (UK) and Cegedim (France). The capsule strength will be used to estimate dose in the Danish national databases. However, the degree of completeness is variable across databases. Imputations for missing values or other methods to describe daily dose will be evaluated (i.e., calculation of defined daily doses).

3.5 OUTCOME(S)

The main outcome of this study is the proportion of off-label use estimated among new users of dabigatran etexilate and their characterisation.

3.5.1 On-label use definition

On-label use is when a medication is used as described in the approved drug label. As of 1 August 2011, the EMA-approved indications for Pradaxa were as follows:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more of the following risk factors:
  - Previous stroke, transient ischaemic attack, or systemic embolism (SEE)

- Left ventricular ejection fraction < 40%
- Symptomatic heart failure, New York Heart Association (NYHA) Class 2 or higher
- Age ≥ 75 years
- Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

A revision of this indication statement was submitted for approval in the EU in September 2013. The revision became effective in December 2013, introducing the following modified indication statement: "Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as prior stroke or transient ischemic attack (TIA); age ≥ 75 years; heart failure (NYHA Class ≥ II); diabetes mellitus; hypertension."

The indication application for treatment or secondary prevention of venous thromboembolism EMA/H/C/00829/II/48G obtained a positive CHMP opinion on 25 April 2014 with the following indication statement: "Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults." During the study period, use associated with these indications will be considered off-label use until Commission Decision. The definition of on-label use will have to consider regulatory label changes that have occurred during the product life cycle with respect to indication and also to contraindications (e.g., addition of dronedarone use to the list of contraindications since 30 August 2012). Therefore on-label use will be defined considering the index date and the appropriate label indication and contraindication applicable during the time period comprising the index date.

Table 3 and Table 4 display the preliminary lists of diseases, conditions, and procedures mapped to the ICD-10-CM codes for identification of the current approved indications. ICD-10-CM codes are used in the Danish national databases and in Cegedim (France); Read codes and ICD-10-CM codes are used in the CPRD (UK). These lists of codes will be used to identify the group of on-label users of dabigatran etexilate in each population. The complete list of codes will be available in the detailed, database-specific study protocol.

Two levels of on-label use will be investigated:

- The first level will include a broad definition based on the main code(s) for the approved clinical indications, e.g., atrial fibrillation.
- The second level will include a more restrictive definition by excluding patients with conditions for which the medication might not be indicated within the broad definition, e.g., valvular heart disease or low-risk patients with non-valvular atrial fibrillation.

Table 3 Preliminary list of diagnoses and corresponding ICD-10-CM codes for identification of new users of dabigatran etexilate for primary prevention of venous thromboembolism following total hip or knee replacement surgery

Disease/condition or procedure	ICD-10-CM description	ICD-10-CM code	Use of codes in indication definitions
Total hip replacement	Presence of artificial hip joint	Z96.64*	Primary code for the broad definition of the clinical indication
Total knee replacement	Presence of artificial knee joint	Z96.65*	Primary code for the broad definition of the clinical indication
Absence of venous thromboembolism between total hip or knee replacement surgery and dabigatran etexilate initiation **	Phlebitis and thrombophlebitis of femoral vein Phlebitis and thrombophlebitis of other and unspecified deep vessels of lower extremities Acute embolism and thrombosis of deep veins of lower extremity Pulmonary embolism	I80.1*; I80.2*; I82.3*; I26*	Sub-group of codes for exclusion of VTE in the restrictive definition within the clinical indication

* = wild card character indicating additional subcodes under this primary code; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification. 2014 version. VTE = venous thromboembolism. Procedural codes will be included based on the dictionary system in place in each database.

** Primary prevention defined as prevention of the first VTE event after the index surgery:

Table 4 Preliminary list of diagnoses and corresponding ICD-10-CM codes to identify on-label and off-label use for stroke prevention in non-valvular atrial fibrillation with dabigatran etexilate

Disease/condition or procedure	ICD-10-CM description	ICD-10-CM code	Use of codes in indication definitions
Atrial fibrillation	Atrial fibrillation and flutter	I48*	Primary code for the broad definition of the clinical indication
Valvular heart disease	Non-rheumatic mitral valve, aortic valve, tricuspid valve, pulmonary valve disorders Endocarditis, valve unspecified Endocarditis and heart valve disorders in diseases classified elsewhere	I34*- I39*	Sub-group of exclusive codes for the restrictive definition within the clinical indication
	Chronic rheumatic heart diseases	I05*-I08*, I09.1	Sub-group of exclusive codes for the restrictive definition within the clinical indication
	Congenital malformations of pulmonary and tricuspid valves Congenital malformations of aortic and mitral valves	Q22*-Q23*	Sub-group of exclusive codes for the restrictive definition within the clinical indication
	Presence of heart valve replacement Presence of xenogenic heart valve	Z95.2*-Z95.4*	Sub-group of exclusive codes for the restrictive definition within the clinical indication

Table 4 (cont'd) Preliminary list of diagnoses and corresponding ICD-10-CM codes to identify on-label and off-label use for stroke prevention in non-valvular atrial fibrillation with dabigatran etexilate

Disease/condition or procedure	ICD-10-CM description	ICD-10-CM code	Use of codes in indication definitions
	Mechanical complication of heart valve prosthesis Mechanical complication of coronary artery bypass graft and biological heart valve graft Infection and inflammatory reaction due to cardiac valve prosthesis	T82.0* T82.2* T82.6*	Sub-group of exclusive codes for the restrictive definition within the clinical indication
Stroke, transient cerebral ischaemia (TIA)	Cerebral infarction; occlusion and stenosis of pre-cerebral or cerebral arteries; TIA; acute, but ill-defined, cerebrovascular disease; sequelae of cerebral infarction	I63*-I66* I69.3* G45	Secondary code to support clinical indication
Symptomatic heart failure	Heart failure	I50*	Secondary code to support clinical indication
Systemic embolism	Arterial embolism and thrombosis	I74*	Secondary code to support clinical indication
Diabetes	Diabetes mellitus	E10*-E11*	Secondary code to support clinical indication
Hypertension	Hypertensive disease	I10*-I15*	Secondary code to support clinical indication
Coronary heart disease	Ischaemic heart disease	I20*-I25*	Secondary code to support clinical indication

* = wild card character indicating additional subcodes under this primary code; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification 2014 version. Procedural codes will be refined based on the dictionary system in place in each database

3.5.2 Off-label use definition

The definition of off-label use of oral dabigatran etexilate outside AF will be based on the use for a disease or medical condition other than the labelled indications and patient sub-groups given in Section 3.5.1. The dabigatran indications approved at the time of the index date will be used to define off-label use for each new user identified in the study period. In the absence of labelled indications, potential off-label use could include, but is not limited to, the following:

- General thrombosis prophylaxis other than hip and knee orthopaedic surgery.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults (CHMP opinion 25 April 2014), until Commission Decision
- Anticoagulation for patients with heart valve replacement or a stent.
- General prophylaxis or treatment of a thrombus in any site.
- Patients with hypercoagulability (e.g., factor V Leiden thrombophilia).

A preliminary list of ICD-10-CM codes to identify these conditions is provided in Table 5. The final list will be included in the detailed, database-specific study protocol. In addition, the set of algorithms to be used as proxies for identification of potential clinical indications will be defined and described in the detailed, database-specific study protocol. These proxies will be based on codes for the presence of certain diseases and clinical conditions and the use of certain medications (e.g., use of other oral anticoagulants).

Because dabigatran etexilate has been approved for use only in adults, any identified use in the pediatric groups of age will be considered off-label. New users of dabigatran etexilate aged younger than 18 years at the index date will be considered in the pediatric population.

The proportion of users with each of the contraindications, including those based on comedications, disease, or severity of conditions, such as patients with severe renal impairment, will be also described. In those databases with laboratory test results available, severe renal impairment will be defined as creatinine clearance < 30 mL/min from directly recorded information of the estimated renal function, as available. For those patients with serum creatinine levels and patient weight available, we might estimate glomerular filtration rate by using the Cockgroft-Gault equation and/or the CKD-EPI equation [R13-5416]. However, it is important to the aware that actual values of laboratory test results will be inconsistently recorded in most databases and data will be limited. We will also capture those patients with ICD-10-CM codes for advanced renal disease—N18.4-N18.6, chronic kidney disease, stages 4 and 5 (severe), and end-stage renal disease—as available in each database according to the coding system and version in place.

Given the different recommended dosage regimens in both the approved and the new indications, new users of dabigatran etexilate will be described according to dose categories, but dose will not be included in the study definition of off-label use based on the first level of on-label indications.

Dose will be incorporated in the definition of off-label use based on the second level, which is a more restrictive definition of on-label use (see Appendix 4). In addition, the proportion of new users within the primary VTE prevention subgroup with one or more follow-up prescriptions after the recommended treatment duration will be described. The follow-up prescriptions will be assessed in the 90-day time window after the index prescription..

Table 5 Preliminary list of diagnoses and corresponding ICD-10-CM codes for identification of potential off-label clinical indications of dabigatran etexilate

Disease/condition or procedure	ICD-10-CM description	ICD-10-CM code	Use of codes in off-label indication definitions
Treatment or secondary prevention of venous thromboembolism	Venous thrombosis Pulmonary embolism	I80.1*, I80.2*, I82.3* I26*	
General thrombosis prophylaxis other than hip and knee orthopaedic surgery	Injuries to the knee and lower leg Fracture of femur	S80*-S89* S72*	In the absence of codes for hip or knee orthopaedic surgery (see Table 3)
Anticoagulation for patients with heart valve replacement or a stent	Heart valve replacement Insertion of coronary stent, bypass anastomosis for heart revascularisation	See codes in Table 4 Z95.1 Z95.5	For stent or aorto-coronary bypass surgery in absence of atrial fibrillation (see Table 4)
General prophylaxis or treatment of a thrombus in any site	Malignancies	C00-C97	In absence of codes in Table 3 or Table 4
Patients with hypercoagulability	Antiphospholipid syndrome	D68.61	In absence of codes in Table 3 or Table 4

* = wild card character indicating additional subcodes under this primary code; ICD-10-CM = International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Clinical Modification.2014 version. Procedural codes will be refined based on the dictionary system in place in each database

3.6 COVARIATES

Assessment of the characteristics of new users at the index date will include the following evaluations:

- Patient demographic and practice characteristics (as available in each database) at index date

- Proportion of patients with specific diseases during the baseline period (1 year prior to the index date) or during the cumulative clinical history
- Proportion of patients tested for renal function during the baseline period and before the first prescription of dabigatran
- Proportion of patients using specific medications during the baseline period

3.6.1 Assessment of clinical history and comorbidities

The presence of the following diseases and conditions of interest will be assessed based on the total cumulative clinical history or the baseline period for each patient at the index date, as available in each database:

- Chronic diseases, particularly those related to atrial fibrillation, including cardiovascular and cerebrovascular diseases, hypertension, and diabetes mellitus.
- Diseases or conditions related to the potential off-label use of dabigatran etexilate such as other heart valve replacement, deep venous thrombosis, pulmonary embolism, and disorders of coagulation (i.e., antiphospholipid syndrome).
- Surgical or percutaneous procedures related to the potential off-label use of dabigatran etexilate such as coronary revascularisation procedures or surgery, general or orthopaedic surgery other than hip and knee orthopaedic surgery. The presence of lower limb fractures will also be evaluated.

A complete list of comorbidities will be developed and included in the detailed, database-specific study protocol.

3.6.2 Assessment of the components of risk prediction scores

Summary risk prediction scores for stroke—such as the $CHADS_2$ and CHA_2DS_2-VASc—have been developed for AF for stratifying patients by risk of stroke and have been shown to correlate with increasing risk of thromboembolism [R10-5332]. European guidelines for AF recommend using the CHA_2DS_2-VASc score to stratify patients and guide antithrombotic treatment strategy [P12-11192]. The following risk factors are components of the CHA_2DS_2-VASc score [R10-5332]:

- Congestive heart failure (or left ventricular dysfunction)
- Hypertension
- Age ≥ 75 years
- Diabetes mellitus
- Stroke (or TIA or thromboembolism)
- Vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque)
- Age 65-74 years
- Sex category

Based on available baseline information, new users of dabigatran etexilate will be characterised according to these components. This might help to investigate differences between on- and off-label uses of the drug.

3.6.3 Assessment of co-medications

The use of prescription medications before the index date will be assessed for the use of cardiovascular medicines as well as other selected medicines. Prior uses of other frequently prescribed oral anticoagulants, such as warfarin or acenocoumarol, and of other antithrombotics (e.g., aspirin) will be evaluated for each index prescription of dabigatran etexilate. A complete list of medications of interest will be developed and included in the detailed, database-specific study protocol.

3.7 DATA ANALYSIS METHODS

The analyses will be descriptive at baseline. Assessment at baseline will include data for the 1 year before the index date, for the definition of the clinical indication, and all available data, for assessment of the prior history of diseases and conditions. All available data might also be used for medications included in the definition of certain proxies for indication. With these data, the following analyses will be performed in each database study:

- Age (including pediatric age) and sex distribution
- Proportion of patients with a prior diagnosis of specific diseases and conditions of interest listed in Sections 3.5 and 3.6
- Proportion of patients with specific types of diseases as listed in Section 3.6 —prior to the index date
- Proportion of patients with renal function test performed during the baseline period and before the first prescription of dabigatran etexilate
- Proportion of patients using specific medications. Use of medications will be based on the 6 months prior to the index prescription.
- In the Cegedim (France) database, all the information from new users of dabigatran etexilate will be described by the type of panel and clinical specialty.

3.7.1 Main analysis by indication

The main analysis will be to estimate (with 95% confidence intervals) the prevalence proportion of off-label use among new users of dabigatran etexilate during the overall study period in each of the study populations. This will include potential off-label clinical indications and contraindications. The proportion of each of the most common off-label use indications will be described among the overall off-label use group. The proportion of identified users in the pediatric age subgroup will be described.

In addition, separately for each approved clinical indication, the risk profile and use of selected drugs among new users of dabigatran etexilate will be described.

The distribution of the dispensed formulation strength or the daily prescribed dose at the index date based on the index prescription will be described, overall and by on-label and off-label indication sub-group. The proportion of new users within the primary VTE prevention subgroup with one or more follow-up prescriptions after the recommended treatment duration will be described. The follow-up prescriptions will be assessed in the 90-day time window after the index prescription.

To evaluate the differences between sub-groups by indication, proportions for categorical variables and means for continuous variables will be estimated (with 95% confidence intervals) within each sub-group. If appropriate, medians will be used instead of means when the variables of interest do not assume a normal distribution.

All the results will be presented for each country-specific database. In addition, for France, all the data will be stratified by type of physician panel: primary care or cardiologist. As part of the analysis, tables presenting the results will be generated. Table shells for the key descriptive analyses will be developed for the detailed, database-specific protocol.

A weighted, pooled prevalence of off-label use among new users of dabigatran etexilate for the entire study population (CPRD, Cegedim, and Danish national databases) will be estimated (with 95% confidence intervals) when the individual results of all three databases are available.

4. STUDY LIMITATION

The design of this study will allow description of new users of dabigatran etexilate and assessment of whether or dabigatran etexilate is prescribed for its authorised indications. The proportion of off-label use in each study population will be estimated, and the characteristics of patients using the drug off-label will be described.

The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis, thereby minimising bias related to differential reporting of prescriptions or impacts of contacts with patients and health care professionals. Although misclassification of clinical indication is recognized as a potential issue for all these databases, studies evaluating data already collected may be the most efficient way to assess potential off-label use. In a prospective study with data specifically collected for this goal, clinicians may be more inclined to align diagnoses with approved indications than when working in their day-to-day clinical care setting.

However, there are a few challenges in the conduct of this study:

- There is a dependency on the level of use of the medications in each country. Furthermore, the lag period of capturing dabigatran etexilate exposure, which ranges from 6 weeks to 12 months across databases, needs to be considered when estimating the availability of study results.
- We are unlikely to be able to evaluate “all” the first-ever dabigatran prescriptions because the first prescription for many patients will likely be prescribed by specialists in outpatient or inpatient settings, rather than by physicians in the primary care setting who will write the follow-up prescriptions. For France, we will be able to describe new users of dabigatran etexilate prescribed by physicians in the primary care setting and by cardiologists in outpatient settings.
- The quantity and quality of the data available might differ among the different databases. For example, information relating to clinical indication or comorbidity might be missing or of insufficient quality in some of the databases.

- None of the databases capture over-the-counter medications.
- Prescription of aspirin for cardiovascular prevention is usually recorded by GPs.
- The degree of recording completeness might be variable across databases for some variables such for laboratory testing.

Logistic and scientific coordination across the research centres will be of critical importance to standardise as much as possible data extraction and analysis under the detailed, database-specific study protocol.

5. STUDY COORDINATION AND DATA MANAGEMENT

RTI Health Solutions (RTI-HS) will lead the program and conduct the study in the UK CPRD. RTI-HS will work collaboratively with the Danish investigators at the University of Southern Denmark for the Danish national databases and French Cegedim Strategic Data research teams to conduct the study. The Danish and French investigators will provide input to the development of the final detailed, database-specific study protocol adapted for each database. The adapted protocols for each database will include the specific list of codes in the coding system and version used in each database.

For statistical analyses, RTI-HS and Cegedim use SAS, and the University of Southern Denmark uses Stata.

6. QUALITY ASSURANCE AND CONTROL

RTI-HS will work closely with the selected database custodians and researchers to establish and ensure a complete alignment of procedures for the project. None of the extracted datasets will contain data that allow identification of subjects included in the study. Each electronic record will be completely anonymised and will not contain any personally identifying data. RTI-HS will work collaboratively with the group of investigators and custodians at the selected databases to ensure a high level of stored data protection according to European regulations. At RTI-HS, all programming will be independently reviewed by one of the RTI-HS statisticians. The study reports will undergo quality-control review, senior scientific review, and editorial review.

7. ETHICAL/SCIENTIFIC APPROVAL AND GOOD PRACTICE

The study will be conducted in accordance with the International Society for Pharmacoepidemiology (ISPE) *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [R09-0182]. The research team will adhere to the 2013 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) methodological standards for study protocols [R13-5419], as documented through the 2013 checklist [R13-1395].

Approval from the RTI-HS institutional review board (IRB) will be obtained. A waiver of individual patient informed consent will be requested due to the nature of this study.

IRB approval and any other reviews required by specific committees will be obtained according to applicable national and local regulations. In addition, the legal and IRB requirements for accessing and using de-identified, individual patient–level data in the selected databases will be followed.

- The CPRD has obtained ethical approval from a Multi-centre Research Ethics Committee (MREC) for this type of observational research using CPRD data. However, approval from the MHRA's Independent Scientific Advisory Committee (ISAC) for database research is required [R14-0016].
- The French Cegedim study will not require any CNIL (Commission nationale de l'infromatique et libertés), National Commission for Data Protection, submission. The longitudinal patient database global process (formerly BKL Consultant, Thalès) was authorised by the CNIL in December 1993 (Receipt 271.306) and renewed on June 20, 2002 (Receipt 271.306 version 2). No further approval is required.
- For the Danish national databases, approval will be requested from the Danish National Board and from the board of the general practitioner database (DAMD).

The study will comply with the definition of the non-interventional (observational) study provided in Article 2(c) of Directive 2001/20/EC and in the EMA *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies* [R13-5420] and the corresponding regulations as applicable in each country where the study is conducted.

8. STUDY MILESTONES AND RESPONSIBILITIES

8.1 NEXT STEPS

Table 6 Study Milestones and Timelines

Milestone	Timeline	Comment
Submission of initial protocol to European Medicines Agency (EMA)	August 2011	Completed
Brief common study protocol adopted by CHMP	October 2012	Completed
Revised common study protocol V3.0 submission to EMA	February 2014	CHMP Request for Supplementary Information (RSI) including PRAC Assessment Report received April 2014
BI responses to RSI including revised study protocol V4.0 submission to EMA	May 2014	
Periodic monitoring of users of dabigatran etexilate in each database	1-2Q 2014	Ongoing

Table 6 (con't) Study Milestones and Timelines

Final database-specific study protocol	Q2 2014	
Ethical and scientific approvals or exemptions	Q2 2014	
Study implementation in each database: when the number of users in each database reaches approximately 5,000[a]	Q2-3 2014 (estimated)	Based on sales estimates
Study status reports (PBRER)	Aligned with PBRER timelines	
Study report	1Q 2016 (estimated)	After completion of analysis in each database

[a] The final study size will depend on the uptake of dabigatran in each country. The study might be initiated with fewer users if uptake is slow in some countries.

8.2 RESPONSIBILITIES

The research team will be integrated by RTI-HS as the coordinating centre and lead for the UK CPRD component, the French Cegedim Strategic Data study research team, and the Danish investigators led by [redacted] at the University of Southern Denmark for the Danish national and general practice databases, with the collaboration of BI epidemiologists.

The financial sponsor of this study is Boehringer Ingelheim GmbH (BI GmbH), the developer and manufacturer of dabigatran etexilate.

9. DISSEMINATION OF STUDY AND RESULTS

As per Module VIII of the 2013 EMA *Guideline on Good Pharmacovigilance Practices (GVP)* [R13-5420], this study will be included in the EU PAS register (Website: encepp.eu/encepp_studies/indexRegister.shtml).

The study status and results will be included in regulatory communications such as the risk management plan and Periodic Benefit-Risk Evaluation Report (PBRER). The final study report will be submitted as a variation application.

Dissemination and communication of findings from this study will be in accordance with the *Guidelines for Good Pharmacoepidemiology Practices (GPP)* [R09-0182] and the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VIII* [R13-5420]. Study

results will be published following the guidelines of the International Committee of Medical Journal Editors [R13-5418].

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P12-11192 Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P; ESC Committee for Practice Guidelines (CPG).
2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. (Erratum in Eur Heart J. 2013 Mar;34(10):790 and Eur Heart J. 2013 Sep;34(36):2850-1) Eur Heart J. 2012 Nov;33(21):2719-47.

10.2 UNPUBLISHED REFERENCES

Not applicable.

11. FUNDING

The study will be funded by BI GmbH.

12. AMENDMENTS AND UPDATES

Note: The protocol is not in the current template in accordance with the *Guideline on Good Pharmacovigilance Practices (GVP) Module VIII – Post-Authorisation Safety Studies* [R13-5420] because the original submission was in 2011; however, we have included the ENCePP checklist in Appendix 2.

- Protocol version 4.0 (dated 16 May 2014) includes the following revisions based on the feedback from the Pharmacovigilance Risk Assessment Committee (PRAC) and CHMP:
  - Revised text on page 8 to "Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (CHMP opinion 25 April 2014), until Commission Decision."
  - Revised Section 7 with clarifications on approvals that need to be requested, by SDU investigators, from the Danish Health Board and the board of the general practitioner database (DAMD).
  - Revised Section 3.5.2 to include the dose of the index prescription in the off-label use definition and the proportion of new users within the primary VTE prevention subgroup with one or more follow-up prescriptions after the recommended treatment duration within 90-day time window after the index prescription (page 26). A diagram has been inserted in Appendix 4 to clarify categories of on-label and off-label use.
  - Pages 7 and 25 have been revised to clarify that the dabigatran indications approved at the time of the index date will be used to define off-label use for each new user identified in the study period.
  - The title and content of Table 3 have been revised to "Preliminary List of Diagnoses and Corresponding ICD-10-CM Codes for Identification of New Users of Dabigatran Etexilate for Primary Prevention of Venous Thromboembolism Following Total Hip or Knee Replacement Surgery.".
- Revisions of protocol version 3.0 (dated 3 February 2014) include label updates and a change in target countries (Denmark instead of Italy) based on reimbursement and dabigatran uptake in each country.
- The revised protocol version 2.0 (dated 8 March 2012) of the original study protocol submitted in August 2011 was adopted by CHMP in October 2012.

13. APPENDICES

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

None.

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMEA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 2)

Adopted by the ENCePP Steering Group on 14/01/2013

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 page number(s) 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). Note, 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).

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	33
1.1.2 End of data collection[2]	☒	☐	☐	33
1.1.3 Study progress report(s)	☒	☐	☐	33
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☒	☐	☐	33
1.1.6 Final report of study results	☒	☐	☐	33

Comments:

The data collection encompasses the time period from the launch of dabigatran etexilate for the prevention of stroke in atrial fibrillation in each country until the target number of new users is reached in each selected country-specific database. Therefore, the start and end of data collection could be different for each country-specific study; they are estimated to occur within 2Q 2014 and 1Q 2016, respectively. Because the original submission of the protocol was in 2011, it is not in the current EMA template, please see the table on page 32-33 for milestones and timelines.

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	10,11
2.1.2 The objectives of the study?	☒	☐	☐	5, 12
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	15-17
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

This is a drug utilization study focused on potential off-label use; therefore, formal hypothesis testing is not applicable.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	6,12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	

[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**	**Page Number(s)**
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

This is a cross-sectional drug utilisation study; therefore, no endpoint will be measured. The main outcome will be the proportion of off-label use. Also, as a descriptive cross-sectional study, we will not measure any effects.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	5,15-17
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6,18
4.2.2 Age and sex?	☒	☐	☐	6,18
4.2.3 Country of origin?	☒	☐	☐	5,15-17
4.2.4 Disease/indication?	☒	☐	☐	19
4.2.5 Co-morbidity?	☒	☐	☐	27
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	6,18

Comments:

This is a cross-sectional drug utilisation study focused on potential off-label use; therefore, seasonality is not of relevance to this study.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	18,20
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	18,20
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?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

This is a cross-sectional drug utilisation study. New users of dabigatran will be described at the initial prescription; therefore, 5.3 to 5.5 are not applicable.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

This is a drug utilisation study to evaluate potential off-label use of dabigatran. The outcome is described on page 20, Section 3.5; endpoints are not applicable by study design.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

This is a drug utilisation study to evaluate potential off-label use of dabigatran. This section does not apply by study design.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	12-17
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☒	☐	☐	12-17
8.2 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)	☒	☐	☐	16
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	12-17; 26-27

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	8, 17
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	6, 12-15
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	12-17

Comments:

The study main outcome is the proportion off-label use. The potential clinical indication will be identified through the disease and procedures dictionaries in place in each database (ICD-10, Read codes, etc.). See corresponding descriptions on pages 20-26, Section 3.5, OUTCOME(S). Endpoints do not apply by study design.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	19,20

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	8-9,28-29
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe the methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

This is a cross-sectional drug utilisation study. New users of dabigatran will be described at the initial prescription therefore 10.1, 10.2, and 10.4-10.6 do not apply.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☐	☐	☒	
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	30
11.3 Are methods of quality assurance described?	☒	☐	☐	30

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	29-30
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	30

Comments:

This is a cross-sectional drug utilisation study; therefore, the proportion of missing information will only be described. No external review is planned. At RTI-HS, all programming will be independently reviewed by one of the RTI-HS statisticians.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	29
12.1.2 Information biases? (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. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	19,20,28
12.3 Does the protocol address other limitations?	☒	☐	☐	29-30

Comments:

This is a cross-sectional drug utilisation study. New users of dabigatran will be described at the initial prescription only.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/ Institutional Review Board approval been described?	☒	☐	☐	30,31
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	30

Comments:

The ethics review will be done prior to implementation of the study as specified in the protocol.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	37

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	33
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	33

Comments:

Name of the main author of the protocol: Cristina Varas-Lorenzo

Date: 15/May/2014

Signature: _____

APPENDIX 3. ATC CODES FOR ANTITHROMBOTIC AGENTS

Table 7 ATC codes for antithrombotic agents

ATC code	Name	Defined daily dose		Route of administration	Note
		Amount	Unit		
B01AA Vitamin K antagonists					
B01AA01	Dicoumarol	0.1	g	Oral	
B01AA02	Phenindione	0.1	g	Oral	
B01AA03	Warfarin	7.5	mg	Oral/Parenteral	
B01AA04	Phenprocoumon	3	mg	Oral	
B01AA07	Acenocoumarol	5	mg	Oral	
B01AA08	Ethyl biscoumacetate	0.6	g	Oral	
B01AA09	Clorindione				
B01AA10	Diphenadione				
B01AA11	Tioclomarol				
B01AA12	Fluindione				
B01AB Heparin group					
B01AB01	Heparin	10	TU	Parenteral	
B01AB02	Antithrombin III	2.1	TU	Parenteral	
B01AB04	Dalteparin	2.5	TU	Parenteral	Anti Xa
B01AB05	Enoxaparin	2	TU	Parenteral	Anti Xa
B01AB06	Nadroparin	2.85	TU	Parenteral	Anti Xa
B01AB07	Parnaparin	3.2	TU	Parenteral	Anti Xa
B01AB08	Reviparin	1.43	TU	Parenteral	Anti Xa
B01AB09	Danaparoid	1.5	TU	Parenteral	Anti Xa
B01AB10	Tinzaparin	3.5	TU	Parenteral	Anti Xa
B01AB11	Sulodexide	500	LSU	Oral/Parenteral	
B01AB12	Bemiparin	2.5	TU	Parenteral	
B01AB51	Heparin, combinations				
B01AC Platelet aggregation inhibitors excluding heparin					
B01AC01	Ditazole				
B01AC02	Cloricromen				

Table 7 (cont'd) ATC codes for antithrombotic agents

ATC code	Name	Defined daily dose		Route of administration	Note
		Amount	Unit		
B01AC03	Picotamide				
B01AC04	Clopidogrel	75	mg	Oral	
B01AC05	Ticlopidine	0.5	g	Oral	
B01AC06	Acetylsalicylic acid	1	tablet	Oral	Independent of strength
B01AC07	Dipyridamole	0.2	g	Parenteral	
		0.4	g	Oral	
B01AC08	Carbasalate calcium	1	tablet	Oral	
B01AC09	Epoprostenol				
B01AC10	Indobufen				
B01AC11	Iloprost	0.15	mg	Inhalation	
		50	mcg	Parenteral	
B01AC13	Abciximab	25	mg	Parenteral	
B01AC15	Aloxiprin				
B01AC16	Eptifibatide	0.2	g	Parenteral	
B01AC17	Tirofiban	10	mg	Parenteral	
B01AC18	Triflusal	0.6	g	Oral	
B01AC19	Beraprost				
B01AC21	Treprostinil	4.3	mg	Parenteral	
B01AC22	Prasugrel	10	mg	Oral	
B01AC23	Cilostazol	0.2	g	Oral	
B01AC24	Ticagrelor	0.18	g	Oral	
B01AC30	Combinations				
B01AC56	Acetylsalicylic acid and esomeprazole				
B01AD Enzymes					
B01AD01	Streptokinase	1.5	MU	Parenteral	
B01AD02	Alteplase	0.1	g	Parenteral	
B01AD03	Anistreplase	30	U	Parenteral	
B01AD04	Urokinase	3	MU	Parenteral	
B01AD05	Fibrinolysin				

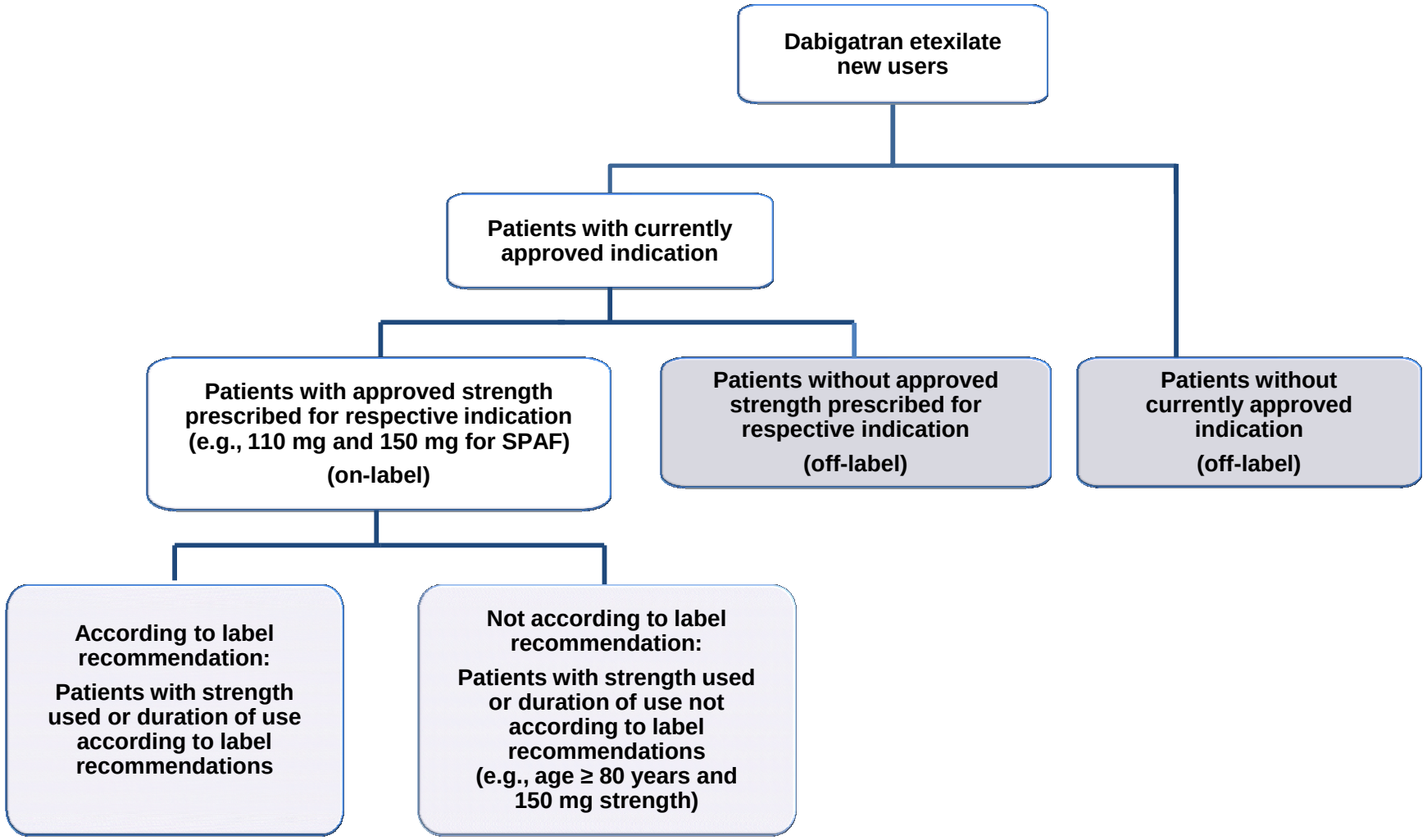
Table 7 (cont'd) ATC codes for antithrombotic agents

ATC code	Name	Defined daily dose		Route of administration	Note
		Amount	Unit		
B01AD06	Brinase				
B01AD07	Reteplase	20	U	Parenteral	
B01AD08	Saruplase				
B01AD09	Ancrod				
B01AD10	Drotrecogin alfa (activated)	40	mg	Parenteral	
B01AD11	Tenecteplase	40	mg	Parenteral	
B01AD12	Protein c				
B01AE Direct thrombin inhibitors					
B01AE01	Desirudin	30	mg	Parenteral	
B01AE02	Lepirudin	0.25	g	Parenteral	
B01AE03	Argatroban	0.2	g	Parenteral	
B01AE04	Melagatran	6	mg	Parenteral	
B01AE05	Ximelagatran	48	mg	Oral	
B01AE06	Bivalirudin	0.25	g	Parenteral	
B01AE07	Dabigatran etexilate	0.22	g	Oral	
B01AF Direct factor Xa inhibitors					
B01AF01	Rivaroxaban	10	mg	Oral	
B01AF02	Apixaban	5	mg	Oral	
B01AX Other antithrombotic agents					
B01AX01	Defibrotide				
B01AX04	Dermatan sulfate				
B01AX05	Fondaparinux	2.5	mg	Parenteral	

g = grams; LSU = lipoprotein lipase releasing units; mcg = micrograms; mg = milligrams; MU = million units: NA = not available; TU = thousand units; U = units.

Source: WHO Collaborating Center for Drug Statistics Methodology. ATC/DDD index: B01A: Antithrombotic agents. World Health Organization. Updated 19 Dec 2013. Available at: website: whocc.no/atc_ddd_index/?code=B01A. Accessed 8 January 2014.

APPENDIX 4. CATEGORIES OF ON-LABEL AND OFF-LABEL USE OF DABIGATRAN



APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Other	[redacted]	19 May 2014 14:46 CEST
Approval-Regulatory Affairs	[redacted]	19 May 2014 14:54 CEST
Approval-Team Member Drug Safety	[redacted]	19 May 2014 15:23 CEST
Approval-EU Qualified Person Pharmacovigilance	[redacted]	19 May 2014 16:56 CEST
Approval-Head Pharmacovigilance	[redacted]	19 May 2014 17:15 CEST
Verification-Paper Signature Completion	[redacted]	20 May 2014 10:20 CEST
Approval-Team Member Medical Affairs	[redacted]	20 May 2014 14:19 CEST
Approval-Therapeutic Area Head	[redacted]	21 May 2014 13:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Other	[redacted]	09 Jun 2014 16:31 CEST