NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

POST-APPROVAL SAFETY STUDY (PASS) OF THE UTILIZATION PATTERN OF APIXABAN IN THE NETHERLANDS

Compound Number:	BMS-562247-01
Compound Name:	Apixaban
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1. INTRODUCTION

Off-label prescription occurs when a practitioner chooses to prescribe a drug in a manner that is inconsistent with the prescribing information approved by the governing regulatory authority. For medicinal products approved by the European Commission, the licensed indications are documented in the Summary of Product Characteristics (SmPC). Examples of off-label prescribing may include, but are not limited to the administration of the drug in doses, routes of administration or for reasons outside of labeled indications, or use in patients who do not meet age requirements, or other criteria as outlined in the label.

1.1. Background and Rationale

Apixaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for:

1) Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery,

2) Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors,

3) Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

These indications, referred to as knee and hip replacement, NVAF, and treatment of DVT/PE, along with the date of approval are shown in Table 1. Use of apixaban outside these indications is a regulatory and safety concern.

To address this concern, the Sponsor proposes two studies describing the utilization of the product in two countries of the European Union (EU): a drug utilization study focusing on off-label use of apixaban in the Netherlands, as described herein, and a second study of apixaban drug utilization in Sweden, which is described in a separate protocol.

The approved SmPC in the Netherlands will be used as the single reference safety document for this study.

Table 1. Indications and Dates of EMA Authorisation

	Abbreviated Indication	Indication	Date of EMA Authorisation
1.	THA/TKA	Prevention of VTE in adult patients who have undergone elective hip or knee replacement surgery	18 May 2011
2.	NVAF	Prevention of stroke and SE in adult patients with NVAF, with one or more risk factors, such as prior stroke or TIA; age >= 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class >= II).	19 Nov 2012
3.	Treatment of DVT/PE	Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.	28 July 2014

DVT: Deep vein thrombosis
NVAF: Non-valvular atrial fibrillation
NYHA: New York Heart Association
PE: Pulmonary Embolism
SE: Systemic Embolism
TIA: Transient Ischaemic Attack
VTE: Venous Thromboembolic Events

2. STUDY OBJECTIVES AND ENDPOINTS

The overall objective of this study is to describe the utilization patterns of apixaban in the Netherlands.

Specifically, the study seeks to:

1. Estimate the proportion of apixaban users in the outpatient settings who receive the drug for the approved indications at the time of the study,

2. Describe the characteristics of the patients who are prescribed apixaban for on-label and off-label indications.

3. STUDY DESIGN

This will be a descriptive study using retrospectively collected data from electronic health record databases. The study will describe the utilization pattern of apixaban during the first three years after launch for the VTE prevention indication in the Netherlands (01 Dec 2011 through 31 Dec 2014).

4. STUDY POPULATION

4.1. Inclusion Criteria

All patients identified in the database who have received an apixaban dispensation during the study period (01 Dec 2011 through 31 Dec 2014) will be included in this study.

4.2. Exclusion Criteria

There is no exclusion criterion. All patients identified in the database who have received an apixaban dispensation during the study period will be included.

5. STUDY TREATMENT AND DURATION

This is a descriptive study assessing the utilization pattern of apixaban in real-world outpatient settings. There is no study mandated dosing or duration requirement.

6. STUDY PROCEDURES

6.1. Data Source

The data source for this study will be the PHARMO medical record linkage system, a population-based, patient-centric data tracking system that includes high-quality and complete information on patient demographics, mortality, drugs dispensed by outpatient pharmacies and a subset of hospital pharmacies, hospital morbidity, clinical laboratory and

pathology findings, and general practitioner (GP) information. Specifically, four databases will be used: the Inpatient Pharmacy Database, Outpatient Pharmacy Database, the Hospitalisation Database, and the GP Database. Information will be captured on apixaban dispensed to hospitalized patients and to patients receiving apixaban from outpatient pharmacies. These prescriptions will be linked to diagnoses and surgeries from inpatient and GP records.

The PHARMO databases cover 3.2 million community-dwelling inhabitants of 65 municipal areas in the Netherlands and are linked via probabilistic linkage methods to form a database network on a patient level. Dispensed drugs are coded using the Anatomical Therapeutic Chemical (ATC) classification system, and medical diagnoses are coded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. The database has been used in previous studies of anticoagulant use and bleeding risk (Penning-van Beest, Erkens et al. 2005; Penning-van Beest, Koerselman et al. 2007; Penning-van Beest, Koerselman et al. 2008).[1, 2, 3]

6.2. Data Compilation Procedure

Patients who received an outpatient pharmacy dispensing of apixaban (prescriptions of GPs and specialist physicians) will be identified as well as patients who were prescribed apixaban in-hospital during an admission.

Hip and knee replacement and other surgeries will be identified via appropriate procedure and ICD-9 codes from linked hospital discharge diagnoses, and by International Classification of Primary Care (ICPC) codes or free text indication field in the linked GP data. The following algorithm will be used to identify the patients who have undergone the elective hip or knee replacement surgery:

- First, procedure codes will be used to identify all patients who have undergone hip or knee replacement surgery within 30 days before apixaban prescription (including total and partial replacement procedures).
- Second, hospital discharge diagnoses (both primary and secondary) will be used to see if these included hip or knee fracture diagnostic codes.
    - If yes, then the hip or knee replacement surgery will be considered non-elective and apixaban prescription off-label.

If the primary or secondary discharge diagnoses do not include hip or knee fracture, then surgery will be considered elective and apixaban prescription on-label.

NVAF and treatment of DVT/PE will be identified using a similar approach**.**

6.3. Decision Rules for Defining On- and Off-Label Use

For the purpose of this study, apixaban prescriptions for the NVAF and treatment of DVT/PE indications will be considered off-label up to and including the date that apixaban received approval for those uses in the EU. Apixaban prescriptions for NVAF and treatment of

DVT/PE indications will be classified as on-label starting on the day after regulatory approval and continuing through the end of the study.

On-label use of apixaban will be defined as a dispensation of the drug to:

1) An adult (ie, 18 years of age or older) and,

2) A patient whose hospital records include:

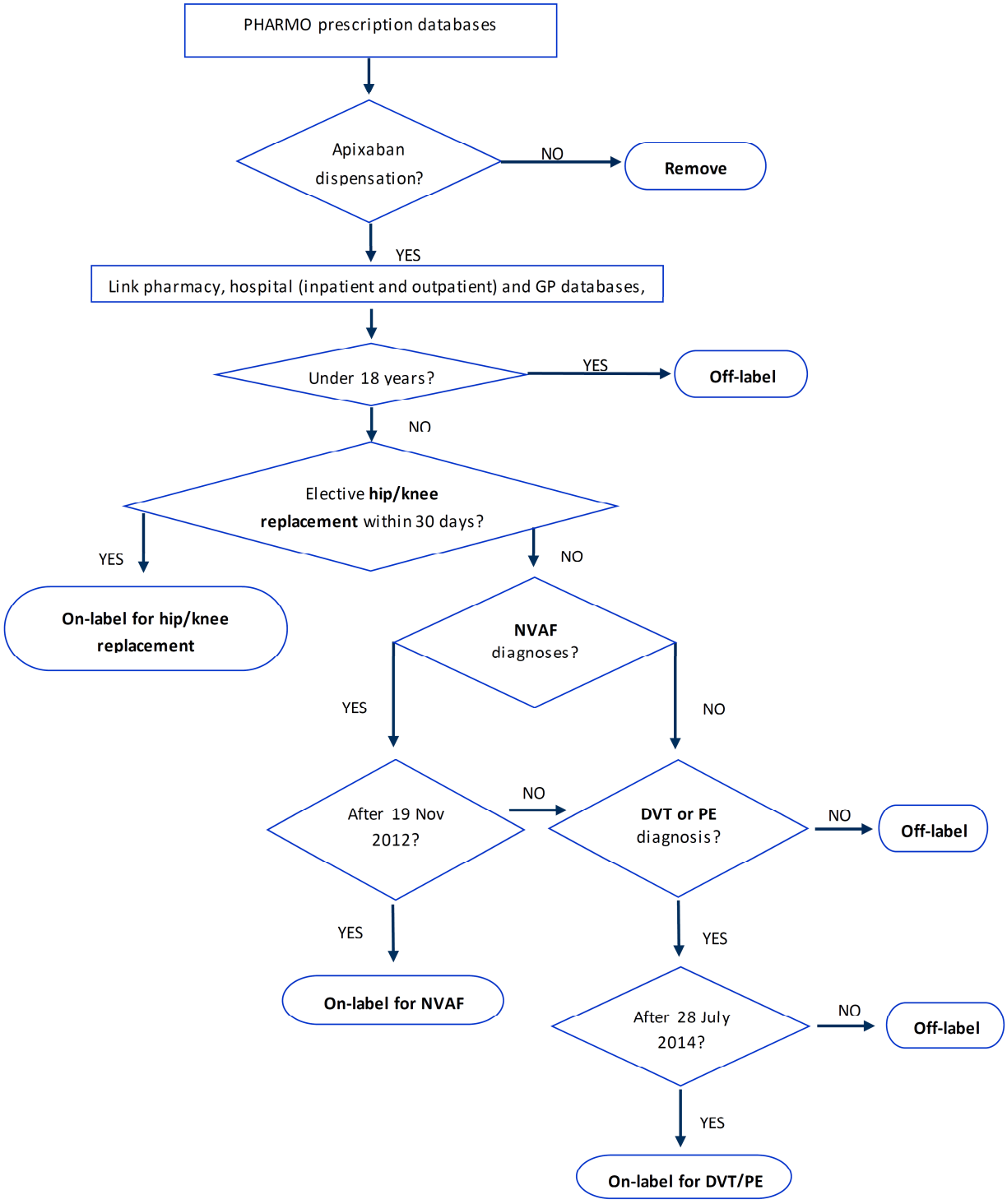
    a) An elective hip or knee replacement within 30 days before the apixaban prescription, or

    b) An apixaban prescription after 19 November 2012 and a diagnosis of NVAF before the apixaban prescription, or,

    c) An apixaban prescription after 28 July 2014 and a diagnosis of DVT or PE before the apixaban prescription (Figure 1).

If during the study apixaban receives approval for any other condition in the Netherlands, the new indication will be considered 'on label' use following the date of approval.

Figure 1: **Flow Chart for Record linkage and On- and Off-label Classification.**



6.4. Data Elements

- Patient demographics: Age and Gender.
- Information on dispensing of apixaban: dispensing date, dose, amount dispensed, duration of use based on amount of drug prescribed.
- Hospital admission information: dates of hospital admission and discharges, ICD-9 discharge diagnoses, surgical procedure codes.
- GP information: ICPC diagnosis codes, and a short free text field in the database with information on the indication.
- Other recently dispensed drugs: ATC code, dispensing date, dose, amount dispensed, use at the time of apixaban dispensing based on amount of drug prescribed.

The operational definitions and coding scheme of the variables will be described in the statistical analysis plan.

7. DATA ANALYSIS/STATISTICAL METHODS

The variables to be collected in this study will be documented in a Statistical Analysis Plan. This document may modify the plans outlined in the protocol; however, any major modifications will be reflected in a protocol amendment.

7.1. Sample Size Calculation

This is a descriptive study of drug usage without any pre-defined hypothesis to be tested. Therefore, no power calculation for a hypothesis test is relevant. All individual patients identified to have received apixaban in the database in the study period will be included in the study without any sampling procedure.

As shown in the table below, 500 apixaban patients with any indication will provide sufficiently precise estimates of on-label use. For instance, if 25% of patients use apixaban off label, the width of the 95% CI for the off-label use percent will be 7.8 percent (Table 2).

Table 2. Precision Around the Off Label Use Proportion Estimates Assuming a Total Sample Size of 500 Patients

Off label use (%)	Width of 95% CI for off label use (%)
5	4.0
15	6.5
25	7.8
35	8.5
45	8.9

The actual numbers will depend on the uptake of the drug following launch.

7.2. Data Analysis

Descriptive analyses of patient level data will be conducted. Patients will be classified as on-label or off-label apixaban users based on their first prescription for apixaban, ie, the index date. The demographic and clinical characteristics of patients identified to have received an apixaban dispensation will be described. The proportion of patients receiving the drug for indications within and outside the approved label in each of the study years will be estimated and any trend over time will be described. From the hospital discharge records, the comorbidities and clinical procedures (eg, surgeries) at the time of or within 30 days prior to the off-label use will be tabulated as the possible indications for the off-label use. If discharge records during this period do not provide possible indications, information from previous discharges will also be tabulated according to the most recent diagnosis. Furthermore, possible switching from other antithrombotic treatments will be investigated based on dispensed prescriptions during the past year. The dose and duration of prescriptions will be summarized where available.

Stratified descriptive analyses by indication will be performed as described below. As the first step, the study will estimate the proportions of all patients in PHARMO databases over the 3-years post-launch period who received apixaban for:

1. VTE prevention following elective hip and knee replacement surgery (on-label indication)

2. NVAF (off-label indication before the approval, and on-label following the approval)

3. Treatment of DVT/PE (off-label indication before the approval, and on-label following the approval)

4. Any other conditions from a list of pre-defined off-label indications, including other types of surgery and history of other diseases (off-label indications). These may include but will not be limited to hip fracture surgeries, general surgeries, gynaecologic and abdominal surgeries, and diagnoses such as cancer, myocardial infarctions, other cardiac conditions, and other hypercoaguable states in which apixaban could be used off-label.

5. Patients with have no evidence of the conditions for on-label use and who cannot be assigned to the list of pre-defined off-label uses will be classified as off-label and unknown.

Data on diagnoses and surgeries made in the out-patient setting are only available through the GP data. As a consequence, information on diagnoses and surgeries made in the out-patient setting is only available for apixaban users with GP available data and unknown for apixaban users without GP data available.

A sensitivity analysis will therefore calculate the percentage of on-label or off-label apixaban users in the subgroup with GP data. This assumes that the availability of GP data is not related to the ratio of on-label or off-label use.

Second, descriptive analyses will be performed in each of the indication strata to summarize:

1. Demographic characteristics of patients and prescriber specialty;
2. Estimated duration of apixaban treatment and dosages used;
3. Concomitant medication use, with the focus on contra-indicated medications;
4. History of treatment with other anticoagulants;
5. Select co-morbid conditions/medical history, such as renal impairment, severe hepatic impairment, congenital or acquired bleeding disorders.

For off-label indication strata, distribution of surgical procedures (other than hip or knee replacement surgery) and diagnoses (other than NVAF and treatment of DVT/PE) that patients had prior to receiving apixaban to infer possible indications that apixaban was used for. For instance, counts and proportions of patients who had other orthopaedic surgery (eg, hip fracture), within 30 days of apixaban prescription will be reported.

In addition to the stratified analyses by indication described above, stratified analysis according to the inpatient and outpatient subgroups will be presented in the PHARMO study reports.

7.3. Interim Analysis

The analysis will be conducted annually for three years. Interim reports will include all data available at the time of the analysis and may not include all the analyses that will be conducted in the final report.

8. DATA COLLECTION AND DATA MANAGEMENT

The details of data collection procedures have been described in Section 6.

8.1. Access to Data

The Sponsor will not have access to health register records at the level of the individual patient but only to tables with aggregated data. In case of an audit from a regulatory authority or Pfizer, the investigator will be able to document the data processing and statistical analysis and thus verify the reported results.

8.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The

study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9. ADVERSE EVENT REPORTING AND SERIOUS ADVERSE EVENT REPORTING

This study includes unstructured data (eg, narrative fields in the database) that will be converted to structured (ie, coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual AE reports.

10. STRENGTHS AND LIMITATIONS

10.1. Strengths:

- The study will use an established database network that collects the variables required to fulfill the objectives. There are strong linkage systems that use different patient characteristics to probabilistically link different data sources. This database network has been used for multiple pharmacoepidemiologic studies, including those of anticoagulant use and bleeding risk (Penning-van Beest, Erkens et al. 2005; Penning-van Beest, Koerselman et al. 2007; Penning-van Beest, Koerselman et al. 2008).[1, 2, 3]

- The database has coverage of all age groups.

- Hospital admission data as well as general practitioner records can be used to obtain information on the indication.

- By repeating the annual analysis over a three-year period after launch of apixaban, the study will provide data on changing trends, if any.

10.2. Limitations:

- Although in principle all admissions are captured in the hospital admission database, small gaps in data collection have been observed and might also occur during the study period. In addition, surgical procedures conducted outside the Netherlands will not be captured. General practitioner records will also be used to obtain information on the indication, however, GP data will not be available for all patients.

- Validation of the data in the database by reviewing individual patients' original medical records will not be possible.

- If the uptake of apixaban use following launch is slow, the study will have relatively small number of patients in the analysis.

- This study is based on healthcare records data being collected by the PHARMO Institute in the Netherlands and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data is beyond the control of the Sponsor and may affect the study timeline.

11. QUALITY CONTROL AND QUALITY ASSURANCE

Investigators are responsible for following their standard institutional procedures to ensure data quality and integrity, including archiving of statistical programs, appropriate documentation of data cleaning and validity for created variables, and description of available data.

12. ETHICS

12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices such as Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences (CIOMS), EMA ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

12.3. Subject Information and Consent

This is a retrospective study of de-identified data from existing databases without any direct enrollment of subjects. Therefore, no informed consent is applicable.

13. COMMUNICATION AND PUBLICATION OF STUDY RESULTS

13.1. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any

patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

14. REFERENCES

1. Penning-van Beest, F., J. Erkens, et al. (2005). "Main comedications associated with major bleeding during anticoagulant therapy with coumarins." Eur J Clin Pharmacol **61**(5-6): 439-444.

2. Penning-van Beest, F. J., J. Koerselman, et al. (2007). "Quantity and quality of potential drug interactions with coumarin anticoagulants in the Netherlands." Pharm World Sci **29**(6): 671-675.

3. Penning-van Beest, F. J., J. Koerselman, et al. (2008). "Risk of major bleeding during concomitant use of antibiotic drugs and coumarin anticoagulants." J Thromb Haemost **6**(2): 284-290.

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