NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

STUDY OF THE UTILIZATION PATTERN OF APIXABAN IN THE NETHERLANDS

Compound Number:	BMS-562247-01
Compound Name:	Apixaban
Study Number:	B0661018
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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 (approval in 2011) for the prevention of venous thromboembolism (VTE) in patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA). Because VTE prevention is the first approved indication of apixaban, use of apixaban outside this indication is a regulatory 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 Summary of Product Characteristics (SmPC) in the Netherlands will be used as the single reference safety document for this study.

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 proportions of apixaban users in the outpatient settings who receive the drug for the approved indication(s) 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 in the Netherlands (01 Dec 2011 through 31 Dec 2014).

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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. 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).

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. THA, TKA, and other surgeries will be identified via appropriate procedure codes and ICD-9 codes from linked hospital discharge diagnoses, and by International Classification of Primary Care (ICPC) codes and free text search in the linked GP data. Atrial fibrillation and other diagnoses will be identified using a similar approach**.**

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6.3. Decision rules for defining off-label use

For the purpose of this study, off-label use of apixaban will be defined as a dispensation of the drug to a child (i.e., <18 years of age) or to an adult whose hospital records do not indicate a TKA or THA within 30 days before the apixaban prescription.

Figure 1 describes the subject identification, record linkage and the decision process.

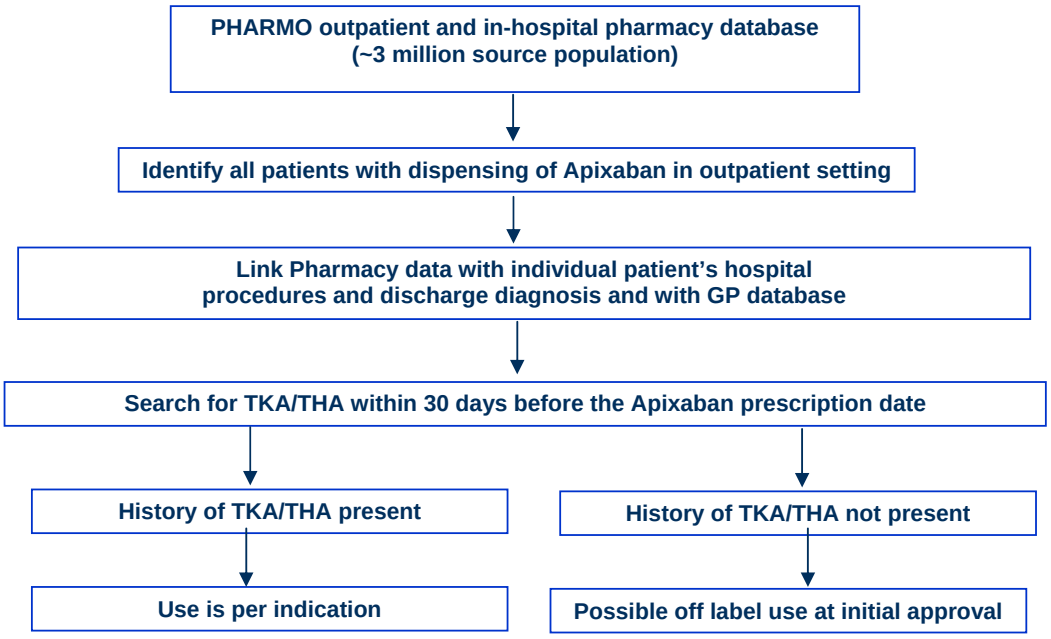

Figure 1. Subject identification, record linkage and the decision process

Additionally, dispensation to minors will be considered off-label use and patients' age at the time of Apixaban prescription will be used to identify such dispensations.

If during the study Apixaban receives approval for any other condition in the Netherlands (e.g., atrial fibrillation) , the new indication will be considered 'on label' use following the date of approval.

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, refill date, repeat prescription.
- Hospital admission information: dates of hospital admission and discharges, , ICD-9 discharge diagnoses, surgical procedure codes..
- GP information: ICPC diagnosis codes, diagnostic information in free text, communications from medical specialists in free text.

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- 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 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. The actual numbers will depend on the uptake of the drug following launch in the Netherlands in December, 2011.

7.2. Data Analysis

Descriptive analyses of the data will be conducted. 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 (e.g., 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 treatment will be investigated based on dispensed prescriptions during the past year. The dose and duration of prescriptions will be summarized where available.

7.3. Interim Analysis

The analysis will be conducted annually for three years.

8. DATA COLLECTION AND DATA MANAGEMENT

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

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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 (e.g., 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 (e.g., 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 uses de-identified patient-level electronic health related databases (e-HRD), in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Furthermore, while the identifiable patient criterion may be met, the identifiable reporter criterion (a particular individual with firsthand knowledge of the identifiable patient) will not. Thus, the minimum criteria for reporting an adverse event (i.e., 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).

- 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.

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- 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

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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

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.

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.

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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