NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

STUDY OF THE UTILIZATION PATTERN OF APIXABAN IN SWEDEN

Compound Number:	BMS-562247-01
Compound Name:	Apixaban
Study Number:	B0661017
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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 Sweden, as described herein, and a second study of apixaban drug utilization in the Netherlands, which is described in a separate protocol.

The approved Summary of Product Characteristics (SmPC) in Sweden 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 pattern of apixaban in Sweden.

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 Sweden (01 Jan 2012 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 Jan 2012 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 at least one 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

Patients using apixaban will be identified from the National Prescribed Drug Register (PDR) which contains information on all drugs prescribed in Sweden that are dispensed to patients outside hospitals, including information about patients, drugs by ATC codes, dates, settings of the dispensing, and the specialty of the prescribing physician. The register is updated continuously with a time lag of 1-2 weeks.

Relevant clinical history for the apixaban users identified from the PDR will be obtained from the National Patient Register (PAR). Patients in the PDR who have used apixaban will be linked to the PAR by a personal identification number (PIN) unique to all Swedish citizens. The PAR contains data from all hospital admissions in Sweden from 1987 to present. At each discharge, information is collected about the patient´s demographics, primary and secondary diagnoses, procedure codes, hospitals and wards of admission, and dates of admission and discharge. Patients who have undergone TKA and or THA will be identified by applicable procedure codes and relevant ICD-10 diagnostic codes. Since 2001, it is also possible to collect the same information from visits to hospital outpatient offices. Information about other diagnoses (e.g., atrial fibrillation) in patients admitted to the hospitals without THA or TKA or visiting hospital outpatient offices will also be retrieved. The register is updated annually and data from the previous year is usually available for analyses in August-September each year after completion of data quality checks.

The databases cover the whole Swedish population of 9.3 million inhabitants. In 2008, about 14,500 primary THA and 4,600 hemi-hip arthroplasties were performed; 78% of the procedures were performed for primary arthrosis. The number of primary TKA was 10,600 in 2008. In addition, re-operations and revisions were also performed. Following an average hospital stay of 4 days, 25% of the patients are discharged to rehabilitation centers or nursing

homes and 75% of the patients are discharged to home. The total number of hip arthroplasties increased by 10% from 2008 to 2010.

Primary care records for apixaban users will be retrieved for the populations of Stockholm County (2.1 million inhabitants, available from 2003) and Västra Götaland County (1.6 million, available from 2006). These records are based on patient contacts to primary care centers and collected in the health administrative databases of each county. This is particularly relevant for the diagnosis of atrial fibrillation, which will likely have incomplete coverage in hospital records.

The total number of persons diagnosed with atrial fibrillation and flutter in inpatient settings in 2010 was 25,672 according to national Swedish health statistics. The overall prevalence of atrial fibrillation has been studied in in a geographically well-defined area of northern Sweden using data from a quality register of anticoagulant treatment and was found to be 2.5% in 2010 (Andersson, Londahl et al. 2012).

6.2. Data Compilation Procedure

Patients who received a prescription for apixaban (identified by ambulatory prescriptions by general practitioner or specialist physician) will be identified. The personal identification numbers of these patients will be used to link to their hospital records. THA, TKA, and other surgeries will be identified via appropriate procedure codes and ICD-10 codes from hospital discharge diagnoses. Atrial fibrillation and other diagnoses will be identified by ICD-10 diagnosis codes in the main or secondary discharge diagnoses as well as in hospital outpatient visit and primary care diagnoses.

6.3. Decision Rule 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 mention a TKA or THA within 30 days before the apixaban prescription.

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

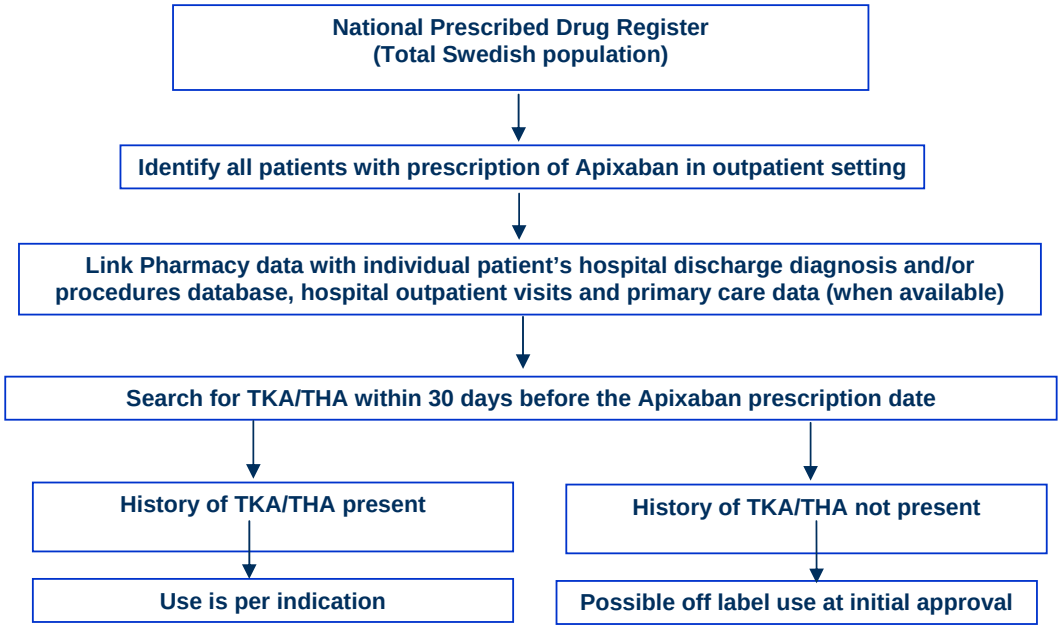

Figure 1. Subject identification, record linkage and the decision process

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 Sweden (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 prescription for 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-10 diagnosis codes in discharge diagnoses, surgical procedure codes.
- Outpatient hospital office visit information: date of visit, ICD-10 diagnosis codes, department type.
- Primary care records from two counties (see above): date of contact, contact type (visit, telephone), ICD-10 diagnosis codes.
- 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.

Based on the Sponsor's projection of number of patients using apixaban in 2012-2014 for prevention of VTE following TKA or THA it is expected that approximately 600 patients will be included in the study. It is projected that up to 13,000 patients with atrial fibrillation (AF) may be included in the study if the AF indication is approved during the study period. However, the actual numbers will depend on the uptake of the drug following launch in Sweden.

7.2. Data Analyses

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.

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 (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 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 that routinely collects information on the variables required to fulfill the objectives. There are strong linkage systems that utilize the unique national identifier of the patients to link different data sources. This database has been used for many pharmacoepidemiologic studies, including those looking at atrial fibrillation and orthopedic surgery populations (Weiss, Stark et al. 2006; Andersson, Londahl et al. 2012).

- The database has coverage of all age groups.

- The database has coverage of all hospital admission and discharge diagnoses.

- 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:

- The study is based on outpatient prescriptions. Therefore patients who receive apixaban only during hospital stay (either for the approved indication or for any off-label indication) and do not refill following discharge will not be included.

- Diagnoses are retrieved from hospital discharge records, outpatient clinic contacts and primary care records available for two counties only (see above). Therefore, information on possible indications may in some cases be missing.

- 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 would have relatively small number of patients in the analysis.

- This study is based on medical records data being collected by the relevant government agencies and county health administrations in Sweden and then accessed by the investigators for analyses. As a result, any unforeseen delay in the collection and compilation of data by one or more of the agencies 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, Investigator 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

Andersson, P., M. Londahl, et al. (2012). "The prevalence of atrial fibrillation in a geographically well-defined population in Northern Sweden: implications for anticoagulation prophylaxis." J Intern Med.

Weiss, R. J., A. Stark, et al. (2006). "Orthopaedic surgery of the lower limbs in 49,802 rheumatoid arthritis patients: results from the Swedish National Inpatient Registry during 1987 to 2001." Ann Rheum Dis **65**(3): 335-341.