The Safety of Oral Apixaban (Eliquis) versus Subcutaneous Enoxaparin (Lovenox) for Thromboprophylaxis in Women with Suspected Pelvic Malignancy; a Prospective Randomized Open Blinded End-point (PROBE) Design.

CV185-394

NCT02366871

Protocol Number: CV185-394
COMIRB Protocol: 15-0187

Clinical Phase: II

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Protocol Version: Version 9, January 27, 2020

PROTOCOL SIGNATURE PAGE

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Investigational Study Coordinating Center:

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Saketh Guntupalli, MD
Date
Principal Investigator/Medical Monitor

I, the undersigned, will conduct the clinical study as described and will adhere to the *Code of Federal Regulations*, Title 21 and Title 45, Part 46, Good Clinical Practice (GCP); International Conference on Harmonization (ICH), and the Declaration of Helsinki. I have read and understood the contents of the Protocol.

The signature of the investigator below indicates acceptance of the protocol and a complete understanding of the investigator obligations as outlined in the protocol.

_____
Investigator Signature

Printed Name: _____ Date: _____

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PROTOCOL SYNOPSIS

Protocol Title:	**The Safety of Oral Apixaban (Eliquis) versus Subcutaneous Enoxaparin (Lovenox) for Thromboprophylaxis in Women with Suspected Pelvic Malignancy; a Prospective Randomized Open Blinded End-point (PROBE) Design. CV185-394**
Site Names and Numbers:	University of Colorado Denver (01)
Research Hypothesis:	Oral apixaban (Eliquis) is as safe and as effective to subcutaneous enoxaparin for the prevention of venous thromboembolism (VTE) in women with gynecologic cancer, following surgery.
Study Schema: **Drugs / Doses /** **Length of Treatment)**	Participants will be randomized to: 1) Oral apixaban 2.5 mg tablet BID for 28 days post-surgery, OR 2) Subcutaneous enoxaparin 40mg QD for 28 days post surgery
Study Objectives: • **Primary:** • **Secondary:**	Primary Objective: To evaluate the incidence of major bleeding (including CRNM bleeding) events in women undergoing surgery for gynecologic cancer with apixaban 2.5 mg BID compared to current standard of care, subcutaneous enoxaparin 40 mg QD for 28 days post surgery. Secondary Objectives: To evaluate the incidence of VTE outcomes, medication adherence rates, quality of life and satisfaction of use for oral apixaban as compared to a subcutaneous injection with enoxaparin.
Study Design:	Prospective Randomized Open-Blinded End-point (Probe) study, phase II study for safety evaluation.
Accrual Goal: **(Total number of subjects)**	400 (1:1 randomization)
Accrual Rate: **(Number of subjects expected per month)**	22/month (total 18 months enrollment)
FPFV: **LPFV:** **Follow Up:** **(dd-mm-yy)**	FPFPFV: 18-05-15 LPLPFV: 15-12-16 Follow Up: 15-03-17

Inclusion Criteria:	For entry into the study, the following criteria MUST be met: 1) Women between 18-89 years of age, 2) Suitable candidate for surgery (meets appropriate performance status, no significant cardiac/renal/hepatic dysfunction), 3) Diagnosis of pelvic malignancy (suspected/confirmed ovarian, endometrial/uterine, cervical cancers, and vulvar cancers) undergoing surgical debulking, 4) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to surgery, 5) Women must not be breastfeeding, WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) apixaban plus 5 half-lives of study drug apixaban (2.5 days) plus 30 days (duration of ovulatory cycle) for a total of 32.5 days post-treatment completion.
Exclusion Criteria:	Women will be excluded if any of the following criteria are met: 1) Malignancy or mass that is non-gynecologic in origin (mass/tumor of origin other than reproductive organ such as rectal, abdominal, breast) 2) Positive pregnancy test on day of surgery, 3) Known history of VTE prior to diagnosis (DVT or PE) due to increased underlying risk of new event 4) Concomitant NSAIDS or other anticoagulant/antiplatelet therapy including ASA >81mg/day, 5) SSRIs and SNRIs (common anti-depressant therapies), 6) Uncontrolled severe hypertension (systolic >200mmHg or diastolic >120 mmHg), 7) With prosthetic heart valves, 8) Active bleeding condition (not limited to: thrombocytopenia, haemophilias, potential bleeding lesions, recent trauma or surgery, recent stroke, confirmed intracranial or intraspinal bleeding), 9) Known or documented bleeding disorders not limited to: anti-phospholipid syndrome, homozygotes for Factor V Leiden deficiency, antithrombin III deficiency, protein C deficiency, Protein S deficiency, hyperhomocystenemia, systemic lupus erythematous, or Prothrombin G2020 gene mutation, 10) Significant renal disease as defined by creatinine clearance less than 30 mL/min, 11) Significant liver disease as defined as AST or ALT twice than normal, 12) Concomitant use of dual strong inhibitors or inducers (CYP3A4, P-gp) 13) Protein C deficiency (increased risk of skin necrosis do those on injectable anticoagulation), 14) Documented allergy to apixaban and/or enoxaparin, 15) Patient's deemed otherwise clinically unfit for clinical trial per Investigator's discretion

Criteria for Evaluation: (safety, efficacy, discontinuation criteria)	**Safety Evaluation:** Assessment of Major Bleeding or CRNM bleeding: Defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site or resulting in death. (CRNM) bleeding events are non-major bleeding events requiring medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or any other discomfort such as pain or impairment of activities of daily life. The time period for development of the outcome is from time initiated study medication until 90 days after surgery. Participants will be asked about any clinical events (i.e. emergency room visit, hospital admission) at visits 3-5; Clinical events (i.e. emergency room visit, hospital admission) will be evaluated for major bleeding outcomes and verified with clinical and laboratory data. Major bleeding events should be documented and study medication should be discontinued immediately and followed per standard of care. **Efficacy Assessments** Assessment of VTEs**:** The time period for development of the outcome is 90 days after surgery. Participants will be assessed at study visits 3-5 and at any unanticipated visits by physical exam of the calves, and symptom assessment for DVT/PE using Wells criteria for DVT scoring and PE screening. Wells criteria for DVT is a validated instrument and used clinical for suspicion of DVT. The Wells criteria has been modified to include screening criteria for detecting PE. Participants exceeding moderate risk, high probability of DVT risk, will be followed for further evaluation with lower extremity Doppler. Participants meeting criteria for PE probability will be followed for further evaluation with spiral CT of the chest. Participants with a VTE should be followed per standard of care after discontinuation of study. Assessment of Death: All deaths will be evaluated by the study investigator and a determination will be made if death is related to the study drug, related to the study outcomes (major bleeding or VTE), or unrelated to study. A composite of VTE-related deaths, among overall VTE outcomes will evaluate safety and risk profiles of the study medication. **Discontinuation Criteria**: Subjects MUST discontinue study medication (for any of the following reasons: • Withdrawal of informed consent (subject's decision to withdraw for any reason). • Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject. • Pregnancy – Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study. – The investigator must immediately notify BMS if a study subject becomes pregnant.

	• Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.
Statistics:	Risk analysis and time-to-event analysis will be conducted for primary (bleeding) and secondary (VTE, minor bleeding, death) endpoints.T-tests and chi-square analyses will be used to compare adherence rates, satisfaction and QOL outcomes. Demographic and baseline characteristics will be used in multivariable risk-analysis of primary and secondary outcomes.

Abbreviations and Definitions of Terms

AE	Adverse Event
ALT	Alanine Transaminase
ASA	Acetylsalicylic Acid (Aspirin)
AST	Aspartate Transaminase
ASCO	American Society of Clinical Oncology
BID	Twice a day
BMS	Bristol-Meyer Squibb
BSO	Bilateral Salpingo-Oophorectomy
CRC	Clinical Research Coordinator
CRF	Case Report Form
CRNM	Clinically Relevant Non-Major
CT	Computed Tomography
DAR	Drug Accountability Record
DILI	Drug-Induced Liver Injury
DSM	Data Safety Monitoring
DSMC	Data Safety Monitoring Committee
DSMB	Data Safety Monitoring Board
DVT	Deep Vein Thrombosis
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HCG	Human Chorionic Gonadotropin
HIPAA	Health Insurance Portability and Accountability Act

HRT	Hormone Replacement Therapy
IDS	Investigational Drug Service
IEC	Institutional Ethics Committee
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
IRB	Institutional Review Board
IT	Information Technology
IUD	Inter-Uterine Device
NCI	National Cancer Institute
NDA	New Drug Application
NIH	National Institute of Health
NSAE	Non-Serious Adverse Event
NSAID	Non-Steroidal Anti-Inflammatory Drug
PE	Pulmonary Embolism
PI	Principal Investigator
PTT	Partial Thromboplastin Time
QD	Once a day
QOL	Quality of Life
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SCD	Sequential Compression Devices
subQ	Subcutaneous
TAH	Total Abdominal Hysterectomy
UCD	University of Colorado Denver
UAE	Unanticipated Event

UAP	Unanticipated Problem
ULN	Upper Limit of Normal
USO	Unilateral Salpingo-Oophorectomy
VTE	Venous Thromboembolism
WOCBP	Women of Child Bearing Potential

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1. INTRODUCTION

Gynecologic cancers (uterine, ovarian, cervical and vulvar) affect nearly 100,000 women in the US each year.[1] While early stage disease of all types achieves high cure rates, women with advanced disease have a poorer prognosis. Typically endometrial and cervical cancer present at an early stage, however nearly 80% of ovarian cancers are detected at advanced stage (> stage I) and have already spread. These cancers become difficult to treat and tend to have the worst survival rates. Even with optimal treatment, most relapse and less than one-fourth of patients survive past 5 years.[2, 3] The standard of care for nearly all gynecologic cancers (early and advanced stage) remains aggressive surgical debulking with resection of all visible disease. The extent of surgical resection to microscopic disease remains the most significant prediction of overall survival, particularly with ovarian cancer.

Surgical debulking for gynecologic cancers varies by disease site, however common to nearly all procedures is hysterectomy, removal of adnexae, removal of lymphatic tissue (pelvic and para-aortic) as well as peritoneal biopsies/omentectomy. These debulking procedures are often aggressive in their nature requiring extended operative times with patients immobile and in a lithotomy position. On average, ovarian cancer debulking procedures may take up to 5 hours to complete. Additionally, gynecologic cancer patients tend to have risk factors which further pre-dispose them to surgical morbidity as they tend to be more obese, have metabolic syndrome (diabetes, hypertension, glucose intolerance etc.) and lead more sedentary life-styles.[4]

Venous thromboembolism (VTE), which includes deep venous thrombosis (DVT) and pulmonary embolism (PE), remains one of the most lethal surgical complications in women who undergo surgery for gynecologic cancer. Because gynecologic tumors grow within the pelvis and involve lymphatic drainage in direct contact with lower extremity vessels, VTE rates are significantly higher in women with gynecologic cancer as compared to other malignancies.[5, 6] Rates of DVT in gynecologic cancer have been reported as high as 26% in untreated women and as high as 9% for PE.[7] Pulmonary embolism is significantly associated with mortality and death may occur in up to 25% of patients that have this complication. Additionally, there is a risk for major bleeding following gynecologic surgery. This risk is ~1% with the standard use of Lovenox following surgery. [8, 9]

The cost to the healthcare system of VTE complications is quite high as these patients require extended anti-coagulation and surveillance for 6 months post-treatment and if a second DVT/PE occurs, lifelong anti-coagulation is necessary. The extended anti-coagulation time adds both financial and resource strain to health care systems as aggressive monitoring and imaging is required for these women to ensure that VTE is not worsening. Because of these rates, the ASCO has developed guidelines for post-operative VTE prophylaxis for women undergoing surgery for gynecologic cancer.[10] These include the use of pre-operative heparin prior to surgery, sequential compression devices (SCD) during surgery and post-surgical DVT prophylaxis including the use of heparin and low-molecular weight heparin.

Current recommendations include 28 days of post-op prophylaxis for these patients with low molecular weight heparin (Lovenox 40mg SQ daily). [11]

For a variety of reasons, the use of subcutaneous low-molecular weight heparin Lovenox has not proven to be ideal. While the drug has been associated with a significant decrease in VTE, the ideal use of this drug has come into question. Common patient complaints of Lovenox use include: injection site reaction, pain with auto-injection, bruising, bleeding, nausea/vomiting and cost. The cost of a 28 day course of Lovenox is an additional barrier to ideal use this drug as this can cost the patient up to $970 for a one month supply, out of pocket.[12] While the actual use rate of women with gynecologic cancers has not been elucidated, data from the orthopedics research observing outpatient prophylaxis, identified an ~60% compliance rate.[13] This places women with gynecologic cancer at significant risk for the development of VTE given the suggested low compliance for prophylaxis treatment, and that their baseline risk of developing a VTE complication is higher than other surgical oncology cases or surgery for benign disease. With Lovenox use in outpatient prophylaxis demonstrating poor adhearence, a more cost-effective and compliant friendly medication could have an impact on VTE outcomes.

1.1 Significance

A more ideal treatment regimen is suggested to be oral anti-coagulation, which could potentially obviate many of these negative effects. In a randomized trial of post-operative DVT prophylaxis, Lovenox was compared to warfarin and subcutaneous (subQ) heparin for the prevention of VTE.[14] Oral anti-coagulation proved to have similar efficacy compared to standard therapy and had significantly lower risks of major bleeding. Additionally, the oral administration led to no titration of levels during outpatient prophylaxis. This study was not specific for gynecologic cancers, in which we know the risks for VTE outcomes are higher. An oral anticoagulant could potentially be more ideal for gynecologic surgical patients to increase adherence, and reduce VTE events. Previous studies have found that apixaban 2.5mg BID provides the greatest benefit-risk profile.[15]

2. STUDY OBJECTIVES

The primary objective of this study is to evaluate the incidence of major bleeding and clinically relevant non-major bleeding events in women undergoing surgery for gynecologic cancer with apixaban 2.5 mg BID compared to current standard of care, subcutaneous enoxaparin 40 mg QD for 28 days post surgery; participants will continue to be followed for 90 days following surgery for bleeding events. Treatment assignment will be stratified for those having minimally invasive versus open surgery.

Secondary objectives of this study include: to evaluate the incidence of VTE outcomes, medication adherence rates, quality of life and satisfaction of use for oral apixaban as compared to a subcutaneous injection with enoxaparin.

2.1 Hypothesis

Oral apixaban (Eliquis) is as safe and as effective to subcutaneous enoxaparin for the prevention of venous thromboembolism (VTE) in women with gynecologic cancer, following surgery.

3. PRELIMINARY STUDIES AND RESEARCH CENTER

Apixaban (Eliquis) is an oral anticoagulant for the treatment and prevention of thromboembolic events. Apixaban is a novel, orally active, potent, direct selective inhibitor of coagulation Factor Xa. It directly and reversibly binds to the active site of Factor Xa and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. It is advantageous as there is no need to perform routine blood monitoring tests including, international normalized ratio (INR), partial thromboplastin time (PTT) and Factor Xa, to determine clotting in participants receiving treatment. Several studies have shown the efficacy of apixaban for the treatment and prevention of VTE.[12, 16-22] Lassen *et al.* demonstrated a non-inferiority when apixaban was compared to lovenox for post-operative DVT prophylaxis in patients undergoing knee replacement, with side effect profiles similar to gynecologic cancer patients. Further, this study found apixaban to be superior to enoxaparin for the prevention of VTE in patients undergoing hip replacement.[18] Phase III studies have continued to demonstrate the efficacy of apixaban for DVT prophylaxis following orthopedic surgery.[20-26] Additional clinical research has found apixaban to effectively decrease the risk of stroke events in patients with atrial fibrillation, changing the standard of care for prevention of major bleeding events in these patients.[27]

Given this impressive treatment profile, we anticipate that the same efficacy could be replicated in the prevention of VTE in women undergoing surgery for gynecologic cancer. An oral-anticoagulant for standard treatment for prevention of VTE outcomes following surgery could help improve the surgical mortalities associated with gynecologic oncology surgical patients, improve patient adherence for outpatient treatment, and reduce VTE surveillance and outcomes.

3.1 Principal Investigator and Research Center

The University of Colorado Division of Gynecological Oncology performs over 600 gynecologic surgical cases a year.[28] About one-half of surgical candidates meet the criteria for minimally invasive surgical procedures over traditional open surgery. Patients are monitored after surgery for bleeding and VTE risks; approximately 10% are hospitalized following surgery because of a DVT/PE event occurring within 28 days after surgery.

Dr. Saketh Guntupalli is a trained gynecologic oncologist and surgeon at the University of Colorado Denver (UCD) whose research interests includes decreasing surgical morbidities for gynecologic cancer patients. The University of Colorado Denver is a clinical research institution and one of the nation's 40 Comprehensive Cancer Centers. UCD is the only National Cancer Institute-designated cancer center serving Colorado and it's surrounding states. The goal of the University of Colorado Cancer Center is to provide cutting edge and nationally recognized clinical and translational research, to discover and shape tomorrow's treatments, and improve survivorship.

3.2 Overall Risk/Benefit Assessment

By taking part in this study, participants will be helping researchers learn more therapies for prevention of VTE following gynecologic surgery for pelvic malignancies. The information obtained from this study will be used provide more consumer-friendly and cost-effective medication therapy for treatment after surgery. The treatment benefits may be comparable to those of standard care. An oral medication may provide patients with an easier and more cost-effective option for treatment after surgery, increasing patient compliance and decreasing overall risk of VTE events.

To Participant: There are known risks for taking anticoagulation post-surgery. However the intent of prophylactic anticoagulation is to reduce the patient's risk of VTE outcomes following surgery and has been standard of care. Current therapies are administered by self-administered injections daily and can be costly for a 1-month supply. An oral medication will provide patients with a more convenient, easier and cost-effective therapy for prevention of VTEs following surgery.

To Society: VTEs are a serious and sometimes fatal outcome. Patients undergoing gynecologic surgery, followed by physical limitations, are at greater risk for VTEs within the first month following surgery. These risks are significantly reduced with anti-coagulation prophylaxis. An oral medication option may decrease overall VTE and fatal VTE outcomes following gynecologic surgery for pelvic malignancies and increase compliance with prophylaxis therapy.

4. OUTCOME MEASURES

4.1 Primary Outcome

The primary outcome of this study is the incidence of major bleeding and CRNM events in women undergoing surgery for gynecologic cancer. Rates of major bleeding events will be compared for apixaban and subcutaneous enoxaparin, stratifying analyses by both surgical intervention groups (minimally invasive versus open). Major bleeding will be assessed at study Visits 3-5.

Major bleeding is defined according to International Society on Thrombosis and Haemostasis (ISTH) criteria as: 1) Fatal bleeding, and/or 2) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, and/or 3) Bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cells.[29] CRNM bleeding events are defined as those events that do not meet the definition of major bleeding but are associated with medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or any other discomfort such as pain or impairment of activities of daily life.

Clinical events (i.e. emergency room visit, hospital admission) will be evaluated for major bleeding and CRNM bleeding outcomes and verified with clinical and laboratory data. Incidence of major bleeding events will compared in the apixaban and enoxaparin groups in the setting of gynecologic surgery. Participants will first be determined to of met a bleeding outcome by assessment during a study visits. Blinded adjudication of bleeding events will then be conducted by a clinician not involved with enrollment for this research study, specifically an oncology surgeon at UCH, meeting all local IRB requirements for conducting research. The unaffiliated clinician will not be aware of subject's treatment assignment. An assessment for major or CRNM bleeding will be made using the criteria outlined in the protocol by the blinded clinician. Blinded classification of the primary endpoint will be used in final analysis. This will decrease misclassification and optimize study efficacy for the major end-point.

4.2 Secondary Outcomes

Secondary outcomes will compare:

1) Incidence of DVT/PE events in apixaban compared to enoxaparin following gynecologic surgery. VTE incidence will also be examined for the stratified surgical intervention sub-categories. Determination of a DVT event will be measured using the Wells

criteria for DVT assessment tool [30] and confirmed by ultrasound; determination of PE will be measured using additional risk criteria adapted from the Wells criteria modified for PE tool [31] and confirmed by chest CT (Appendix 1). Participants will be evaluated using the VTE assessment at study visits 3-5 and at any unanticipated study visits. Participants meeting the criteria for high probability of VTE will be followed for ultrasound or chest CT confirming VTE suspicion. All participants are expected to meet criteria for moderate risk by satisfying Wells criteria: 1) having an active cancer and 2) major surgery within 4 weeks. Any participant exceeding moderate risk criteria will be further evaluated for VTE. Incidence of VTE outcomes resulting in death will be evaluated in the safety analyses.

2) Medication adherence rates will be measured using two methods; self-reported adherence as recorded in participant diaries, and return of all (unused and used) medication bottles for evaluation. Diaries and medication bottles will be collected and reviewed at Visits 3 and 4. Adherence will be compared between the two methods. Participants must meet 93% compliance to be considered compliant to taking the assigned treatment medication. This will be determined by missing a total of four pills of the apixaban or two injections of enoxaparin, regardless of if consecutive missed doses or not. If participants, miss more than two days of medication, we will re-contact them, over the phone or in clinic, to further follow up on why they were non-compliance. This could be after the 90 day follow up.

2b) Participant compliance will also be measured by looking at the costs of lovenox injections that were dispensed by the outpatient pharmacy to patients. The out of pocket costs to the patients will be collected because they will be reimbursed by the study. Insurances cost of lovenox before out of pocket cost and zip codes (distance to clinic) will be collected to assess the correlation with non-compliance.

3) Satisfaction will be measured at completion of drug administration using a brief questionnaire administered at Visit 4 (Appendix 2). Additionally, comments/complaints associated with taking the assigned treatment medication will be assessed using participant diaries..

4) Quality of Life (QOL) will be measured using a validated instrument SF-8 health survey (Appendix 3). Both a baseline (Visit 0) and a post-treatment (Visit 4) assessment will be conducted. The SF-8 provides metrics for functional health and well-being and is appropriate for use across all disease areas.

Demographic and clinical data will also be collected in order to describe the study population and determine differences among the randomized groups. Demographic and clinical data will be verified against the participant medical records to assure data completion and minimize missing data in our analysis.

Demographic data will include: name, medical record #, contact information, date of birth, age, race and ethnicity. Identifying information (name, medical record # and contact information) will not be entered into the database and will only be used by research site to verify data, access medical records, and contact the patient for study visits. A log will be kept with their identifiable data and participants will be linked to their study chart by study ID.

Clinical Data will include: menopause status, cancer diagnosis, surgical intervention, pre-existing medical conditions, concomitant medications, allergies, and vitals (blood pressure, pulse, temperature, respiratory rate, height, weight, BMI).

5. ETHICAL CONSIDERATIONS

5.1 Good Clinical Practice

This study will be conducted in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50).

The study will be conducted in compliance with the protocol. The protocol, any amendments, and the subject informed consent will receive Institutional Review Board/Independent Ethics Committee (IRB/IEC) approval/favorable opinion before initiation of the study.

All potential serious breaches must be reported to The University of Colorado IRB immediately. A serious breach is a breach of the conditions and principles of GCP in connection with the study or the protocol, which is likely to affect, to a significant degree, the safety or physical or mental integrity of the subjects of the study or the scientific value of the study.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure; debarment).

5.2 Institutional Review Board

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, consent form, subject recruitment materials/process (eg, advertisements), and any other written information to be provided to subjects. The investigator or sponsor should also provide the IRB/IEC with a copy of the Investigator Brochure or product labeling information to be provided to subjects, and any updates.

The investigator should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

The University of Colorado Denver will provide study monitoring and audit to study sites, requiring direct access to source data and documents. Continuing review will be conducted per institutional guidelines. The study will remain open with the local IRB until notification from coordinating site to close the study. All correspondence with local IRB should be maintained in the study regulatory files. The sponsor may request additional audit of study sites.

5.3 Informed Consent

Investigators must ensure that subjects or, in those situations where consent cannot be given by subjects, their legally acceptable representative are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

Investigators must:

1) Provide a copy of the consent form and written information about the study in the language in which the participant is most proficient prior to clinical study participation. The language must be non-technical and easily understood.

2) Allow time necessary for subject or subject's legally acceptable representative to inquire about the details of the study.
3) Obtain an informed consent signed and personally dated by the participant or the participant's legally acceptable representative and by the person who conducted the informed consent discussion.
4) Obtain the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other information to be provided to the subjects, prior to the beginning of the study, and after any revisions are completed for new information.
5) If informed consent is initially given by a subject's legally acceptable representative or legal guardian, and the participant subsequently becomes capable of making and communicating their informed consent during the study, then consent must additionally be obtained from the participant.
6) Revise the informed consent whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the subject or the participant's legally acceptable representative or legal guardian, of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

6. INVESTIGATIONAL PLAN

6.1 Study Design and Duration

This study will employ a PROBE (prospective randomized open blinded end-point) clinical trial design. This is a phase II open-label study to determine and the safety of a less invasive anticoagulation therapy following gynecologic surgery (comparing apixaban to standard of care, subcutaneous enoxaparin). Potential participants will be identified through the gynecological clinical practices prior to gynecologic surgery and will be randomized (1:1) to one of the study medications. Randomization will be stratified for surgical intervention (minimally invasive vs. open).

Participants will be randomized to one of the following by the inpatient clinical pharmacy staff:

1) Oral apixaban 2.5 mg tablet BID for 28 days post-surgery, or
2) Subcutaneous enoxaparin 40mg QD for 28 days post surgery

Participants will be followed for 90 (± 7 days) days post-surgery for bleeding and VTE outcomes. Study events will be documented on the study clinical research forms (appendix 5) for each visit. The study will continue to enroll all suspected gynecologic cancer patient undergoing surgery at the participating institutions until the enrollment goal of 200 participants per arm (N=400) has been met.

6.2 Description of Population to be Enrolled

All patients with a suspected or confirmed diagnosis of pelvic malignancy undergoing surgical debulking (ovarian, endometrial/uterine, cervical cancers, vulvar cancers) will be eligible for enrollment. Suspected gynecologic malignancy includes patients with a pelvic mass, pre-cancerous lesions of the gynecologic tract, patients with an elevated serum CA125, and vulvar/cervical lesions. Confirmed gynecologic malignancy includes patient with histologic

diagnosis confirmed by pathologic review of an ovarian, uterine, cervical or vulvar cancer. This includes cytologic review of ascites. Suspected malignancies can take up to 7 days to determine if the resected surgical specimen is indeed a cancer. The current standard of care is continue treatment for patients even if they have suspected malignancy. Inclusion into the study will include women 18-89 years of age at one of the participating gynecological cancer centers during the enrollment period.

6.2.1 Inclusion Criteria

For entry into the study, the following criteria MUST be met:

1) Women between 18-89 years of age,
2) Suitable candidate for surgery (meets appropriate performance status, no significant cardiac/renal/hepatic dysfunction).
3) Diagnosis of pelvic malignancy (suspected/confirmed ovarian, endometrial/ uterine, cervical cancers, and vulvar cancers) undergoing surgical debulking,
4) Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to surgery,
5) Women must not be breastfeeding, WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug (s) apixaban plus 5 half-lives of study drug apixaban (2.5 days) plus 30 days (duration of ovulatory cycle) for a total of 32.5 days post-treatment completion.

6.2.2 Exclusion Criteria

Women will be excluded if any of the following criteria is met:

1) Malignancy or mass that is non-gynecologic in origin (mass/tumor of origin other than reproductive organ such as rectal, abdominal, breast
2) Positive pregnancy test on day of surgery,
3) Known history of VTE prior to diagnosis (DVT or PE) due to increased underlying risk of new event
4) Concomitant NSAIDS or other anticoagulant/antiplatelet therapy, including ASA >81mg/day
5) SSRIs and SNRIs (common anti-depressant therapies),
6) Uncontrolled severe hypertension (systolic >200mmHg or diastolic >120 mmHg),
7) With prosthetic heart valves,
8) Active bleeding condition (not limited to: thrombocytopenia, haemophilias, potential bleeding lesions, recent trauma or surgery, recent stroke, confirmed intracranial or intraspinal bleeding),
9) Known or documented bleeding disorders not limited to: anti-phospholipid syndrome, homozygotes for Factor V Leiden deficiency, antithrombin III deficiency, protein C deficiency, Protein S deficiency, hyperhomocystenemia, systemic lupus erythematous, or Prothrombin G2020 gene mutation,
10) Significant renal disease as defined by creatinine clearance less than 30 mL/min,
11) Significant liver disease as defined as AST or ALT twice than normal,
12) Concomitant use of dual strong inhibitors or inducers (CYP3A4, P-gp)
13) Protein C deficiency (increased risk of skin necrosis do those on injectable anticoagulation),
14) Documented allergy to apixaban and/or enoxaparin,
15) Patient's deemed otherwise clinically unfit for clinical trial per Investigator's discretion.

Other Exclusion Criteria

- Prisoners or individuals who are involuntarily incarcerated.
- Individuals who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria.

6.2.3 Reproductive Status

For women of reproductive status, Investigators shall counsel WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy Investigators shall advise WOCBP who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% when used consistently and correctly.

At a minimum, subjects must agree to the use of one method of highly effective contraception as listed below:

Highly effective methods of contraception include:

- Male condoms with spermicide
- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs such as Mirena®) by WOCBP subject.
- IUDs, such as ParaGard®
- Tubal ligation
- Vasectomy

  Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female participants must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

6.2.4 Women of Child Bearing Potential

Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a urine or serum Human Chorionic Gonadotropin (HCG) test to confirm absence of pregnancy. WOCBP who will not be sterile following surgery must agree to highly effective contraception for the duration of treatment with study drug (s) apixaban plus 5 half-lives of study drug apixaban (2.5 days) plus 30 days (duration of ovulatory cycle) for a total of 32.5 days post-treatment completion.

6.3 Recruitment and Consent

Recruitment and consent will be conducted in the clinical offices of the gynecological practices participating in this study or in the inpatient pavilion following surgery. Participants will be provided informed consent and HIPAA consent by trained clinical research staff that has completed competencies for clinical research, including HIPAA compliance and GCP. All

participating research staff will have to provide documented proof of meeting these competencies prior to conducting study procedures, including consent. Potential participants will be provided adequate time to review the study procedures and consent and be provided time to ask any questions or concerns they may have. Participants will be made aware that participation is voluntary and they can withdraw from study at anytime. If a participant withdraws from study, they may be prescribed anticoagulation per standard clinical care if still being monitored for post-surgical outcomes. Participation or decision to not participate will not alter a patient's surgical and treatment plan. Participants will not receive compensation for participating in this study.

6.4 Discontinuation of Participants from Treatment

Participants MUST discontinue study medication (for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Pregnancy
  - Instruct WOCBP to contact the investigator or study staff immediately if they suspect they might be pregnant (eg, missed or late menstrual period) at any time during study participation. Institutional policy and local regulations should determine the frequency of on-study pregnancy tests for WOCBP enrolled in the study.
  - The investigator must immediately notify BMS if a study subject becomes pregnant.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical (eg, infectious disease) illness.

All subjects who discontinue should comply with protocol-specified follow-up procedures outlined in Section 8 STUDY ASSESSMENTS AND PROCEDURES. The only exception to this requirement is when a participant withdraws consent for all study procedures or loses the ability to consent freely (i.e., is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness). If a participant withdraws before completing the study, the reason for withdrawal must be documented appropriately.

7. TREATMENTS

Study Medications include:

1) Oral apixaban 2.5 mg tablet BID for 28 days post-surgery, or
2) Subcutaneous enoxaparin 40mg daily for 28 days post surgery.

7.1 Study Treatment: Apixaban

Product Description:

Product Description and Dosage Form	Potency	Primary Packaging (Volume)/ Label Type	Appearance	Storage Conditions (per label)
Apixaban tablet	2.5 mg	Bottles of 60/ Marketed label	yellow, round, biconvex, film-coated tablets with "893" debossed on one side and "2½" on the other side.	Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F)

Definition of Investigational Product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is apixaban.

Definition of Non-Investigational Product: Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care. In this protocol, the non-investigational products are Enoxaparin.

7.1.1 Investigational Drug Service (IDS) Pharmacy

The IDS pharmacist will be responsible for the tracking and reporting of investigational drugs. The IDS pharmacist will be available to the investigator to meet and perform Pre-Site and Study Initiation visits as requested by the study sponsor. The IDS Pharmacist will be available to the study sponsor for the monitoring of study conduct and for study closure. The sponsor will be responsible for providing all study medication and all costs for providing mediation.

The IDS Pharmacist will provide the necessary training to the Pharmacy Department staff that will assist in dispensing investigational drugs.

The study investigator will be responsible for ordering study drug for both in-patient and upon discharge using the standard medical chart request procedures.

7.2 Handling and Dispensing

The investigational product should be stored in a secure area according to local regulations. The investigator is responsible for ensuring that it is dispensed only to study subjects and only from official study sites by authorized personnel, as dictated by local regulations.
If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

7.2.1 Dispensing and Labeling of Investigational Drugs

Dispensing of Investigational Drugs: The Investigational Drug Service dispenses investigational drugs for a variety of inpatient and outpatient research protocols.

Protocol specific Dispensing Guidelines are developed that describe the procedures required for investigational drug management and dispensing.

The Principal Investigator is responsible for obtaining all regulatory and institutional approvals prior to generating an order requesting the dispensing of investigational medications. The Principal Investigator is responsible for obtaining subject informed consent prior to requesting the dispensing of investigational medications.

The IDS will require the receipt of an appropriate physician's order from an authorized prescriber prior to dispensing investigational medications.

Labels for inpatient investigational unit dose and bulk medications will contain the following:

- Subject information that includes:
  - Subject Name
  - Visit and Medical Record Number
  - Location
  - Date
  - Rx Number
  - Drug Name, Dose, and Frequency
  - Space for Technician/Pharmacist's Initials
- Study specific information on the label may include:
  - IRB Number and Abbreviated Study Title (Required)
  - The Statement: For Investigational Use ONLY (Required)
  - Subject Study Number
  - Subject Weight

Labels for outpatient investigational drug prescriptions will contain the following:

- Pharmacy Name, Address and Phone Number
- The Statement: "CAUTION: NEW DRUG Limited By Federal Law To Investigational Use."
- Subject Name and Study ID Number
- Date Dispensed
- Prescription Number
- Directions including Route and Frequency if Applicable
- Name of Drug (All possible components if blinding is required) and Dose
- Quantity Dispensed
- Principal Investigator
- IRB Number

7.2.2 Disposal of Investigational Drugs

The study sponsor will determine the disposal requirements for the investigational drug. The following options are available:

- The IDS Pharmacy can retain used containers at the site. After audit by the sponsor, the used containers are destroyed on site. Appropriate documentation of local destruction will be generated and retained in the study file.
- Used containers are not retained for audit by the sponsor and are destroyed after dose/medication preparation. *Note: Used investigational drug containers containing biohazardous or cytotoxic agents will be appropriately destroyed after use. Retaining these materials would be a contamination hazard for UCH personnel and facilities.*
- The same options are also applicable for unused investigational drugs.

- Medication bottles that are dispensed to the participant and returned to the clinical research coordinator will be maintained in lock cabinets in the clinical research office (with limited access) until audited by the sponsoring institution. Medication will be destroyed after all audits from the sponsor is complete.

Classification of materials for on-site destruction.

- Common Trash will be disposed of by Environmental Services and consists of the following:
    - Empty containers (no pourable waste) of non-biohazardous drugs.
    - Extraneous packaging materials will be considered common trash.
    - Any subject identifiers must be removed or obliterated prior to disposal in common trash.
- Documents with subject identifiers will be disposed of in Security Containers that are located within the Department of Pharmacy.
- Pharmaceutical Waste will be disposed of following guidelines developed by the Hospital Safety Officer. Pharmaceutical waste will be placed into a "Chemo Safety Container for Trace Chemotherapy Waste". Pharmaceutical waste consists of non-cytotoxic, non-biohazardous investigational drug materials (capsules, tablets, topical products, liquids, etc.) in opened or unopened containers (subject returns or undispensed product).
- Trace-Contaminated Cytotoxic or Biohazardous Waste will be disposed of following guidelines developed by the UCH Safety Officer. Pharmaceutical waste will be placed into a "Chemo Safety Container for Trace Chemotherapy Waste". Trace-Contaminated Cytotoxic or Biohazardous Waste includes vials, ampoules, and containers that contain less than 3% or their original contents (i.e. empty).
- Bulk Cytotoxic or Biohazardous Waste will be disposed of following guidelines developed by the UCH Safety Officer. Pharmaceutical waste will be placed into a container labeled for "Storage for Bulk Cytotoxic Waste". Bulk Cytotoxic or Biohazardous wastes include full or partially full vials/ampoules or containers that have greater than 3% of their original contents.

7.3 Drug Ordering and Accountability

Drug Procurement may be accomplished by:

- Bristol-Meyers Squibb (BMS) will send the drug supplies directly to the Pharmacy.
- Investigational drugs will be procured by the IDS pharmacist:
    - Additional supplies of study medications will be requested when existing inventories fall below a predetermined stock level or, if at the rate of current usage, the drug supply will be exhausted before the next inventory period.
    - Additional supplies of study medications will be requested when existing inventories are labeled to expire and replacement supplies are necessary.

7.3.1 Drug Receipt

Receiving Drug: Upon the receipt of investigational drugs the IDS pharmacist will:

- Review the packing slip or drug receipt acknowledgement to determine which protocol the drug is intended.
- Inventory the drug in the shipment and confirm that the contents match the description on the packing slip or drug receipt acknowledgement.
- If the drug is labeled with an expiration date, the date will be noted on the IDS Pharmacist's calendar.
- The drugs will be appropriately labeled with the protocol number and study title. This

will be accomplished by specifically labeling the drug product or by placing the drug into a labeled bag container.
- The required storage conditions will verified by reviewing the drug labeling and the drug will be stored under the appropriate and secure conditions.
- The quantity of received drug will be documented on the appropriate Drug Accountability Record following the instructions provided in the Dispensing Guideline notebook.
- Complete the required acknowledgement procedures. Receipt documents will be filed the study file located in the IDS office.

Quarantine of Drug: If the investigational drug that was received was unsuitable for use, the drug will be quarantined and stored under labeled storage conditions. BMSwill be notified and the drug will be clearly labeled as “Quarantine: Do Not Use”. Release from quarantine will occur only after receipt of written documentation from BMS Written documentation will be retained in the study file located in the IDS office.

7.3.2 Drug Storage and Temperature Monitoring

Investigational drugs will be stored in a secure area where access by unauthorized personnel is limited.
- All investigational drugs will be stored separate from commercial drugs.
- Investigational drugs are protocol specific and will be clearly labeled with the following:
    - The IRB Protocol Number
    - The Protocol Title
    - The Investigator Name
    - Any additional auxiliary labeling deemed necessary by the IDS pharmacist

A locked door will secure the pharmacy area where investigational drugs are stored with access controlled by Pharmacy staff. Satellite dispensing areas are permitted for investigational drug storage and dispensing. Satellite dispensing areas must meet the standards for segregation from commercial product, labeling, security and temperature monitoring.

Temperature Monitoring
- A thermometer that meets the ISO9001 standards for calibration will be used to measure the temperature range for investigational drug products.
- When a thermometer reaches its calibration due date it will be replaced.
- The Certificate of Calibration will be retained on file in the IDS office.
- Temperature ranges will be documented daily on the Temperature Controlled Storage Units Log when the area is staffed. The temperature range on the thermometer will be cleared after the range has been recorded.
- Temperature ranges will not be documented on days where the area is not staffed (i.e. weekends and holidays). The temperature range recorded on the next business day will be the temperature range from when the device was last cleared (i.e. the previous business day when the range was recorded).
- Temperature deviations
    - Will be noted on the Temperature Controlled Storage Units Log.
    - Immediate action will be taken to notify Engineering Services to correct the failure that has lead to the deviation.
    - The deviation will be reported to the study sponsor.

- Drugs will be quarantined until released by the study sponsor.
- Drugs that are not released by the study sponsor will be replaced and will not be used.
- Documentation regarding the deviation and its resolution will be retained in the study file for the impacted protocol.

7.3.3 Accountability and Records Retention IDS

Accountability procedures will document the receipt, dispensing, and disposition of all investigational drugs received

- The Investigational Drug Accountability Record (NIH/NCI OMD No. 0925-0240) will be the standard document that will record investigational drug receipt, dispensing, and disposition.
- The Investigational Drug Accountability Record (DAR) will be protocol and drug specific.
- The protocol specific Dispensing Guidelines developed for a study will clearly describe the required drug accountability procedures.

Inventory Quality Assurance

- Each time a drug accountability transaction is performed the physical count and the DAR count will be confirmed.
- Discrepancy resolution will be done on the DAR or as a note to file.
- Expiration dates (if applicable) of investigational products will be placed on the IDS pharmacist's calendar when they are received. When audits are performed, the expiration dates will be monitored and confirmed.
- An inventory audit of the IDS service will be performed at least annually.

Records Retention: Federal regulations require that records be retained for at least two years after the IND is terminated or an NDA is approved. Multinational studies require that records be retained for at least 15 years after the study is closed.

- At study closure, the Dispensing Guidelines and study file will be archived.
- The archived records will be stored at least three years in the IDS office.
- After being stored for at least three years in the IDS office, the archived files will be transferred to off-site storage following the Storage and Retrieval of Documents and Equipment Department Guideline (080-010). When the Record Storage Request is completed the Destruction Date Required will be 15 years from the date the records are sent to storage.
- The IDS Pharmacist will maintain an electronic file that will have the location of archived records.

7.4 Treatment Assignment

Participants will be randomized 1:1 to either apixaban 2.5 po BID for 28 days after surgery versus enoxaparin 40mg SQ for 28 days after surgery. Block randomization will be used to equally distribute treatment assignment for surgical intervention groups (minimally invasive versus open surgery).

Randomization will occur by our inpatient pharmacy staff at study visit 2 (day 0 or 1-7 days post-op), prior to initiating any study medication. Randomization will be pre-determined using randomization statistical application and entered into the IDS Pyxis for distribution. Participants will be randomized to either receive enoxaparin versus apixaban beginning on

post-operative day 1-7 (Visit 2). The participant will receive the assigned treatment directly from the IDS while in-patient and then receive remaining treatment doses upon discharge, to be continued until visit 3. The statistician responsible for the interim and statistical analysis for this study will be blinded as to which arm is investigation and which is control in the database.

7.4.1 Dosage and Administration

The participant will receive study medications directly from the IDS, Treatment should be continued for 28 days post-randomization. Any standard of care medication will be prescribed through the in-patient pharmacy while in-house and given a prescription for remaining doses upon discharge. Participants will be responsible for taking the medication as prescribed and record taking the medication in the subject diary provided to the participant. Apixaban is an oral medication that should be taken 2x a day, approximately every 12 hours. The enoxaparin is an injectable medication that should be taken 1x a day, approximately the same time every day. Participants must return all empty/unused study medication bottles/vials to the study coordinator at visit 4. Participant adherence will be measured by measure of un-used prescribed medication.

Participants will also record time of day of study medication administration on their participant diary log in addition to any other medications they take during their study enrollment period (appendix 6). Self-report of medication adherence will be compared to adherence determined by medication bottles for verification. If participants, miss more than two days of medication, we will re-contact them, over the phone or in clinic, to further follow up on why they were non-compliance. This could be after the 90 day follow up.

Participant compliance will also be measured by looking at the costs of lovenox injections that were dispensed by the outpatient pharmacy to patients. The out of pocket costs to the patients will be collected because they will be reimbursed by the study. Insurances cost of lovenox before out of pocket cost and zip codes (distance to clinic) will be collected to assess the correlation with non-compliance.

Apixaban should not be used if a patient has active pathological bleeding.
If a dose of apixaban is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and then continue with twice daily administration as before. The dose should not be doubled to make up for a missed dose.
Apixaban can be taken with or without food.
Because there are no data in patients undergoing dialysis, apixaban is not recommended in these patients. Apixaban is not recommended in patients with severe hepatic impairment

7.4.2 Temporary Discontinuation of Apixaban

Discontinuing anticoagulants, including apixaban, for active bleeding, elective surgery, or invasive procedures places patients at an increased risk of thrombosis. Lapses in therapy should be avoided, and if anticoagulation with apixaban must be temporarily discontinued for any reason, therapy should be restarted as soon as possible.

7.5 Concomitant Treatment

All concomitant treatments will be recorded on the participant's study case report form (CRF) to be entered into the electronic database, including the name of the drug, start and stop dates

and reason for use from the time of informed consent through end of trial participation. Any investigational medication will be stopped three months before the start of treatment. Other medication for the treatment of inter-current medical conditions will be permitted and recorded on the participant's diary and recorded as detailed above.

7.5.1 Prohibited and/or Restricted Treatments

Coadministration of apixaban is not recommended with drugs that increase the risk of bleeding (eg, other anticoagulants, heparin, thrombolytic agents). Exclusionary medications include: other anti-coagulation/anti-platelet or NSAIDS therapies, SSRIs and SNRIs (common anti-depressant therapies); avoid concomitant use of apixaban with strong dual inhibitors, or inducers of CYP3A4 and P-gp).

7.5.2 Other Restrictions and Precautions

If possible, apixaban should be discontinued 2 to 3 days prior to elective surgery or invasive procedures. If surgery or invasive procedures cannot be delayed, exercise appropriate caution taking into consideration an increased risk of bleeding. This risk of bleeding should be weighed against the urgency of intervention.

The concomitant use of apixaban with antiplatelet agents increases the risk of bleeding. In patients with atrial fibrillation and a condition that warrants mono or dual antiplatelet therapy, a careful assessment of the potential benefits against the potential risks should be made before combining this therapy with apixaban.

Use apixaban with caution when co-administered with non-steroidal anti-inflammatory drugs (NSAIDs), including ASA regimens > 81mg/day.

7.6 Treatment Compliance

Participants will be randomized to either apixaban 2.5 mg pill taken orally, BID for 28 days after surgery versus enoxaparin 40mg subQ QD for 28 days after surgery. Adherence will be assessed at study visit day 12 (V3) and at end of treatment visit (V4) by review of medication logs and assessment of returned medication containers. Compliance measures by participant self-report will be compared to compliance rates measured by medication return for verification. Participants not missing greater than 2 days of medication, a 93% adherence, will meet compliance. If participants, miss more than two days of medication, we will re-contact them, over the phone or in clinic, to further follow up on why they were non-compliance. This could be after the 90 day follow up.

Participant compliance will also be measured by looking at the costs of lovenox injections that were dispensed by the outpatient pharmacy to patients. The out of pocket costs to the patients will be collected because they will be reimbursed by the study. Insurances cost of lovenox before out of pocket cost and zip codes (distance to clinic) will be collected to assess the correlation with non-compliance.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1 Time and Events Schedule

Procedures and Visit Schedule

Recruitment and Screening	• Provide Informed Consent o Participant receives signed copy of consent • Determine Eligibility o Suspected/Confirmed malignancy o No history of VTE event Not currently on anticoagulant therapy, NSAIDS, SSRIs or SNRIs o Does not have uncontrolled hypertension (systolic >200mmHg or diastolic >120mmHg) o Does not have any known or active bleeding disorders o No prosthetic heart valve o No Protein C deficiency o No concomitant use of strong dual inhibitors/inducers o No known contraindication to study medications • Collect demographic data
V1 **Pre-Op** **1-30 days prior to Surgery**	• Standard of Care Pre-Op exam including: o Pregnancy test if under 45 years of age o Evaluation for renal disease (creatinine clearance <30mL/min o Evaluation for liver disease (AST or ALT more than 2x normal) Vitals and Physical exam o Determination fit for surgery • Collect history and concomitant medications • Quality of Life (SF-8) survey* *SF-8 will be administered after consent, including if consented post-operatively • Surgery to be scheduled within 1-7 days
Surgical Day	• Heparin at 5,000 units SQ 30 mins prior to surgery • SOC procedures for risk reduction (as appropriate): o Pneumatic compression device on the legs during surgery o Heparin 5, 000 units subQ TID for post-surgery starting 6-8 hours after surgery and continued as necessary
V2 Randomization: **Day 1 (1-7 days post-op)**	• Prior to randomization, determine no major bleeding, CRNM bleeding and VTE event occurred since time of consent (do not randomize if **ha**d major bleeding/VTE since surgery). • Participant randomized to oral apixaban 2.5 mg bid or subcutaneous enoxaparin 40 mg for 28 days (1 time per day) • Participant receives training on taking/storing medication • Participant receives training for completing medication and AE diaries • Dispense of study medication via the Research Pharmacy/IDS
Study Days 1-28	• Participant takes medication regimen daily for 28 days, starting on study day 1

	• Participant completes medication and AE logs daily
V3 Study **Day 12 ± 4 days** **Clinical 2 week Post-Op visit**	• Post-op visit per standard of care • Vitals per standard of care • Confirm final cancer diagnosis • Assessment of major bleeding and CRNM bleeding • Assessment of VTE (DVT or PE event) • Review medication adherence and AEs • Discontinue study if VTE event is confirmed
V4 End of Treatment **Day 28 (±4 days)**	• Vitals and Physical exam • Assessment of major bleeding and CRNM bleeding • Assessment of VTE (DVT or PE event) • Review medication adherence and AEs • Quality of Life (SF-8) survey • Participant satisfaction survey • Return all medication bottles (empty and unused) for assessment of adherence
V5 Follow-up **Day 90 (± 2 weeks)**	• Standard of care 3-month post-op visit • Vitals per standard of care • Confirm any hospitalizations/ED visits since last visit • Assessment of major bleeding and CRNM bleeding • Assessment of VTE (DVT of PE event) • Completion of study
Unanticipated Visit **(Suspected Bleeding/VTE)**	• Assessment of major bleeding and CRNM bleeding • Assessment of VTE (DVT or PE event) • Vitals collected • Review medication adhearance and AE • If Bleeding/VTE is confirmed, discontinue from study

Participant will be discontinued if at any time hospitalized for major bleeding, VTE event and/or has a contradiction to assigned medication

Completion of study visits will be documented on the study Clinical Research Forms (CRF) found in Appendix 5.

Recruitment: Potential participants will be recruited from the gynecologic oncology clinical service while being seen for diagnosis and consideration of gynecologic surgery. Potential participants will be approached by the clinical research coordinator or the research investigators for consent into the study. Following informed consent, participants will be provided a copy of the signed consent. For patients who have an emergency surgery or patients with unclear cancer diagnosis and who are appropriate candidates for prophylaxis following gynecologic surgery, they may be recruited post-operatively prior to initiating any study specific procedures.

Screening: Participants will be screened and determined eligible for the study by meeting all inclusion criteria and no exclusion criteria listed in section 6.2 prior to enrollment. Screening conduct may be done in accordance with pre-op surgery visit (V1). After screening and consent, demographic data will be collected on the screening CRF form. The investigator will review the eligibility criteria and verify participant meets all criteria. The investigator should sign the screening documentation, verifying eligibility prior to randomization.

Visit 1: Confirm participant continues to meet all study eligibility criteria outlines in section 6.2. After eligibility is confirmed, participants will complete a pre-op exam per standard of care. Pre-operative assessments should be conducted 1-30 days prior to scheduled surgery. The pre-op exam will include review of the following:

- Negative pregnancy test if pre-menopausal (conducted day of surgery)
- Evaluation for renal disease (creatinine clearance <30mL/min
- Evaluation for liver disease (AST or ALT more than 2x normal)
- Vitals and Physical exam
- Determination fit for surgery

Additional research procedures will include:

- Collection of concomitant medications
- Review of medical history (cancer diagnosis, other medical conditions, allergies)
- Completion of QOL survey SF-8 (this should take ~5 minutes to complete)*

*SF-8 will be administered after consent, including if consented post-operatively

The study coordinator will complete the V1 clinical research form (CRF). The participants will schedule her surgery per clinical standard practice.

Surgery: Surgery will be conducted per standard of care as appropriate. The standard medical protocol for prevention of VTE during surgery include the following procedures:

1. All participants will receive heparin at 5,000 units SQ approximately 30 min before the initiation of surgery, per standard of care.
2. All participants will receive pneumatic compression devices on the legs 30 min before surgery, per standard of care.
3. Post-surgery participants will receive heparin 5000 units subQ for post-surgery starting 6-8 hours after surgery and continue thru 1 day post-op or discharge (which ever is sooner). Participants should not start additional anticoagulant treatments till after post-surgical standard of care therapy has ended.

Risk reduction protocol may be adjusted as appropriate per the provider's discretion. The study coordinator will complete the surgical day CRF, verifying medication provided during surgery and verifying surgical intervention.

Visit 2 visit: Prior to randomization, participant will be assessed for major bleeding events and VTE. If it is determined participant had experienced a major bleeding or VTE event since time of surgery, the participant should not be randomized and should be managed per standard of care. Participant randomization will be conducted 1-7 days after surgery. This will be study day 1. Participants will be randomized to either oral apixaban 2.5 mg bid or subcutaneous enoxaparin 40 mg qd for 28 days by the research pharmacy. The study medication should not be initiated until study day 1 since the participant will still be on heparin post-surgery. The study coordinator will provide participant with medication bottles for the study period and instruction on taking and storing medication for the duration of the study. Distribution of study medication will be recorded on study CRFs. The study coordinator will also provide participant with study diaries and instruction on completing the medication and AE diaries daily. The study coordinator will complete the V2 CRF at time of study visit.

On Study day 1 participants will initiate study treatment regimen apixaban 2.5mg, BID versus enoxaparin 40mg subQ QD, daily for POD 28.

Study days 1-28: The participant should begin taking study medication on study day 1. Participant will be administered the study medication by hospital staff during their in-patient stay. Upon discharge, participants will take the study medication daily as instructed. The

apixaban is an oral medication that should be taken 2x a day, approximately once in the morning and once in the evening. The enoxaparin is an injectable medication that should be taken 1x a day, each morning. Participants should record time of day that they took the medication in subject diaries.

Visit 3/Post-op visit: Participant will return to the gynecologic clinic approximately 2 weeks following surgery (study day 12 +/- 4 days) for a post-op visit. A post-op exam, vitals, confirmation of final diagnosis (based on pathology), and assessment of bleeding and VTE should be conducted per standard of care. The research coordinator will complete the V3 CRF and VTE assessment CRF. For those meeting high probability of VTE, the visit will be followed appropriately by ultrasound or chest CT for confirmation. The research coordinator will review medication adhearance and any AEs since last visit with the participant. Study participation will be discontinued at this time if major bleeding or VTE is confirmed.

Visit 4/End of Treatment visit: Participants will return to the gynecologic oncology clinic for an end of treatment research visit approximately 4 weeks after surgery (study day 28 +/- 4 days). At this visit the following will be conducted:

- Vitals and Physical exam
- Assessment of bleeding events
- Assessment of VTE (DVT or PE event)
- Review of medication and AE diaries
- Quality of Life (SF-8) survey
- Participant satisfaction survey
- Return all medication bottles (empty and unused) for assessment of adherence.

The research coordinator will complete the V4 CRF and a VTE assessment form. For those meeting high probability of VTE, the visit will be followed appropriately by ultrasound or chest CT for confirmation. The research coordinator will collect and review subject surveys and diaries. The research coordinator will also collect all used and unused medication bottles and document return of study medication. Study participation will be discontinued at this time if major bleeding or VTE is confirmed. Participant will be scheduled to return for a follow-up at 90 days (+/- 2 weeks). The participant will not continue study medication or subject diaries for the time between study days 29-90.

Visit 5/Follow-up: Participants will return to the gynecologic oncology clinic approximately 3 months post-op (study day 90 ± 2 weeks). Post-op milestones will be determined per standard of care 3 month follow-up. The study coordinator will collect vitals, assess for bleeding events, conduct VTE assessment, and verify any AEs since last visit. The research coordinator will complete the V5 CRF and a VTE assessment form. For those meeting high probability of VTE, the visit will be followed appropriately by ultrasound or chest CT for confirmation. The participant will be notified of study completion at this time.

Unanticipated Visit: If a patient shows signs of a VTE (pain in leg, warmth in skin, visible veins not normally visible, leg fatigue, severe chest pain, heart rate >100bpm, or hemoptysis) or are determined to have a suspected/confirmed bleeding or VTE event per evaluation, the participant will come to the gynecologic oncology clinic for a unanticipated visit (UAE visit). Vitals will be collected. Participant will undergo an assessment for bleeding and VTE and review of study medications. The research coordinator will complete the UAE visit CRF along with the VTE assessment form. For those meeting high probability of VTE, the visit will be followed appropriately by ultrasound or chest CT for confirmation. If a VTE is confirmed, study

participation will be discontinued. This visit may be conducted in-patient if the participant has been admitted for suspected/confirmed bleeding or VTE.

8.2 Duration

Participants will be followed for 90 days post surgery. Study medication will be taken for the first 28 days of the study. Study participation will end at the completion of the 90-day study visit, or earlier if a serious major bleeding or VTE outcome is reached.

If participant is discontinued early, the study coordinator should make every effort to complete the End of Treatment visit (V4). Reason for early withdrawal/study drug discontinuation must be documented on the early discontinuation CRF.

8.3 Discontinuation of Participants

Participant will be discontinued from study if hospitalized for a bleeding or VTE event (DVT or PE) and/or has a contraindication to their assigned treatment medication. End of Treatment visit will be conducted at time participant is discontinued from the study. Reason for discontinuation should be documented on the early discontinuation CRF.

For participants discontinued from the study early, they will resume normal medical care. Treatment of major bleeding or VTE event will be per standard of care. If participant stops taking their medication prior to being discontinued or ending treatment by the investigator, they may be at increased risk for VTE or bleeding than if they stayed on the medication. This will be outlined in the participant consent. Participants stopping study medication early will be urged to continue taking medication or to return to the clinic for an end of treatment assessment.

8.4 Safety Assessments

Assessment of Major Bleeding event

Major bleeding events are defined as clinically overt bleeding accompanied by a decrease in the hemoglobin level of at least 2 g/dl or transfusion of at least 2 units of packed red cells, occurring at a critical site (intracranial, intraocular, intraspinal, intra-articular, intramuscular with compartment syndrome, pericardial, retroperitoneal), or resulting in death.[29] Clinically relevant non-major (CRNM) bleeding events that don't meet the definition of major bleeding but are associated with medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or any other discomfort such as pain or impairment of activities of daily life.

Major bleeding is a known risk associated with the use of anti-coagulants following major surgery. The time period for development of the outcome is 90 days after surgery. Participants will be assessed for major bleeding in time since surgery prior to randomization. Participants should not be randomized (and should be discontinued from the study) if a major bleeding event is indicated at V2. Participants will be asked about any clinical events (i.e. emergency room visit, hospital admission) at visits 3-5. [29]). Clinical events (i.e. emergency room visit, hospital admission) will be evaluated for major bleeding outcomes and verified with clinical and laboratory data. Major bleeding events should be documented and study medication should be discontinued immediately. Participants with a major bleeding event should be discontinued from the study and followed per standard of care after discontinuation of study.

8.5 Efficacy Assessments

Assessment of VTEs will be conducted using the study VTE assessment form. VTE assessment will be conducted at visits 3-5, and at any unanticipated visits. The study investigator should review all VTE assessments for determination of study continuation.

8.5.1 Assessment of VTE Event

VTE event is a known risk following gynecologic surgery and occur in ~10% of patients without preventative medication. Use of anti-coagulation therapy for 1 month following surgery may reduce risk to ~3%. VTE can be fatal. VTE events should be documented and study medication should be discontinued immediately. Participants should be determined as having no VTE events (assessed per standard of care) at V2 prior to randomization; participants should not be randomized if experiencing VTE at V2. VTE study assessment will be conducted at visits 3-5. Participants meeting high probability for VTE will be followed with ultrasound or chest CT for confirmation. Participants with a VTE should be followed per standard of care after discontinuation of study.

The time period for development of the outcome is 90 days after surgery. Participants will be assessed at study visits 3-5 by physical exam of the calves, and symptom assessment for DVT/PE using Wells criteria for DVT scoring and PE screening [30, 31] (Appendix 1). Wells criteria for DVT is a validated instrument and used clinical for suspicion of DVT. The Wells criteria has been modified to include screening criteria for detecting PE. Participants will all meet moderate risk using Wells criteria due to the following indications: active cancer, major surgery within 4 weeks. Participants exceeding moderate risk, high probability of DVT risk, will be followed for further evaluation with lower extremity Doppler. Participants meeting criteria for PE probability will be followed for further evaluation with spiral CT of the chest.

8.5.2 Assessment of Death Event

All deaths will be evaluated by the study investigator and a determination will be made if death is related to the study drug, related to the study outcomes (major bleeding or VTE), or unrelated to study. Any death related to the study drug should be immediately reported to the local IRB, coordinating site and the sponsor per protocol. Deaths related to bleeding, VTE outcome and unrelated deaths should be reported to local IRB, the coordinating site and the sponsor per protocol. A composite of VTE-related deaths, among overall VTE outcomes will evaluate safety and risk profiles of the study medication.

8.6 Other Assessments

8.6.1 Adherence will be measured by number of days participant took medication. This will be assessed by participant diary and return of empty and unused medication (pill and/or syringe bottles) at V3 and V4. Adherence rates will be compared between treatment arms. Compliance will be indicated by an adherence rate of 93%, or not greater than 2 missed days of medication) If participants, miss more than two days of medication, we will re-contact them, over the phone or in clinic, to further follow up on why they were non-compliance. This could be after the 90 day follow up.**8.6.2 Satisfaction** will be measured using participant questionnaire obtained at End of Treatment. Data will be analyzed qualitatively and quantitatively to describe satisfaction associated with use of each treatment regimen.

8.6.3 Quality of Life (QOL) will be measured using the validated SF-8 instrument, QOL will be collected both at the enrollment visit and the end of treatment visit. Both intra

and inter analysis will be conducted to examine changes in QOL after treatment and compare differences between the two treatment arms in QOL outcomes.

8.7 Study Materials

Bristol-Meyers Squibb (BMS) will provide apixaban 2.5 mg at no cost for this study. Investigator prescribing information and patient information brochures for apixaban are included in appendix 7 and 8. Patients should receive the patient information brochure at study enrollment.

9 ADVERSE EVENTS

9.1 Protection Against Risks

Study staff will obtain all necessary Good Clinical Practice (GCP) and human protection HIPAA training to oblige to such standards for maintaining participant's privacy. Participant study information will be maintained in a locked office and in a secure electronic database with limited access. Electronic databases will only be stored on University secure servers and backed up per regular University IT protocols. REDCap, a secure data collection system, will be used to capture data.[32] REDCap tools provide the highest possible degree of assurance that data will be secure. The University IT department also provides encrypted email services to internal and external recipients. Any study information communicated among the research staff will be done using the encrypted University email service.

9.2 Adverse Events

An Adverse Event [AE] is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition in a patient or clinical investigation subject administered an investigational (medicinal) product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all AEs. The causal relationship can be one of the following:
Related: There is a reasonable causal relationship between study drug administration and the AE.
Not Related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events).

Adverse events that are not serious should be documented in the study AE log, subject study charts, and reported to the local IRB and coordinating site as appropriate. The coordinating site will review AEs at interim analysis.

9.3 Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see *NOTE**: below for exceptions)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.

Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

**NOTE: The following hospitalizations are not considered SAEs:*

- Admissions for anti-cancer therapy in the absence of any other SAE.
- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an “important medical event” or a life-threatening event)
- Elective surgery planned before signing consent
- Admissions as per protocol for a planned medical/surgical procedure
- Routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than remedying ill health state that was planned before study entry. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason)

Participants experiencing a SAE should be discontinued from the study medication if the SAE is related to bleeding, a VTE event and/or a contraindication to the study drug. Participants discontinued from the study medication should be followed per clinical standard of care. SAEs should be documented on the AE CRF and reported to local IRB and the coordinating site within 48 hours of notification of event.

9.3.1 Serious Adverse Event Collecting and Reporting

Following the subject’s written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur during the screening period and within 30 days of discontinuing dosing. If applicable, SAEs must be collected that relate to any later protocol-specific procedure (such as follow-up skin biopsy).

The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
An SAE report should be completed for any event where doubt exists regarding its status of seriousness.
If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy, or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
SAEs, whether related or unrelated to the study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on the SAE Report Form; Pregnancies on a Pregnancy Surveillance Form.
SAE Email Address: Worldwide.Safety@BMS.com
SAE Fax Number: 609-818-3804
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report.
All SAEs should be followed to resolution or stabilization.

9.3.2 SAE Reconciliation

The investigator will reconcile the clinical database SAE cases transmitted to BMS Global Pharmacovigilance (GPV&E). Frequency of reconciliation will be done every three months and once prior to study database lock. BMS GPV&E will e-mail upon request from the investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the investigator determines a case was not transmitted to BMS GPV&E, the case will be sent immediately.

9.3.3 Health Authority Reporting (US FDA IND)

Investigators must adhere to local Health Authority Reporting Requirements. For studies conducted under an investigator sponsored US FDA IND, provide details of the following:

- Any event that is both serious and unexpected must be reported to the Food and Drug Administration (FDA) as soon as possible and no later than 7 days (for a death or life-threatening event) or 15 days (for all other SAEs) after the investigator's or institution's initial receipt of the information.
- BMS will be provided with a simultaneous copy of all adverse events filed with the FDA. SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/.

MedWatch SAE forms should be sent to the FDA at:
MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787
Fax: 1-800-FDA-0178 (1-800-332-0178)
http://www.accessdata.fda.gov/scripts/medwatch/

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology

Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

9.4 Non-Serious Events

A non-serious adverse event is an AE not classified as serious.

9.4.1 Non-Serious Adverse Events (NSAEs) Collecting and Reporting

The collection of non-serious adverse event (NSAE) information should begin at initiation of study drug. Non-serious adverse event information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate.

Non-serious Adverse Events are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

9.4.2 Anticipated Risks

While the study anticipates minimal risks, the following outlines any potential minimum risk to subjects:

i. Breach of Confidentiality: Data obtained using information from medical records, poses minimum risk. All procedures in which information is being obtained will be conducted per standard of care. There is a risk that a patient's privacy may not be protected. This risk is uncommon.

ii. Discomforts: Persons taking anti-coagulation medicine may experience the following: nausea, bruising, headache and bleeding. Additionally, anti-coagulation medication administered by injection may cause bruising and/or soreness at the injection site. This risk is rare occurring in <3% of persons taking either medication.

iii. Contraindications: Persons taking anti-coagulation medicine may experience hypersensitivity or an allergic reaction to the medication. These symptoms may include itching, a skin rash, or difficulty breathing. This risk is rare occurring in <1% of people taking the study medications.

Participation in this study will not have any influence on the patient's current treatment. The study may include risks that are unknown at this time. The investigational medication, apixaban, has not been studied in the setting of women undergoing gynecologic surgery.

9.5 Laboratory Test Abnormalities

The following laboratory abnormalities should be captured and reported as appropriate:

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, use the term anemia rather than low hemoglobin value). Laboratory test abnormalities are provided to BMS via annual safety reports (if applicable), and interim or final study reports.

9.6 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for subject safety).

The investigator must immediately notify WorldwideSafety@BMS.com of this event via the Pregnancy Surveillance Form within 24 hours and in accordance with SAE reporting procedures.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on a Pregnancy Surveillance Form.

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy may also be collected on the Pregnancy Surveillance Form.

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (eg, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

9.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as SAEs.

9.8 Adverse Events of Special Interest

In this study, the following adverse events are to be reported to BMS, regardless of whether these reports are classified as serious or unexpected.

- Potential or suspected cases of liver injury including but not limited to liver test abnormalities, jaundice, hepatitis or cholestasis.

9.9 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious adverse event, as appropriate, and reported accordingly.

10 DATA COLLECTION AND MONITORING

10.1 Data Collection Tools

Data will be collected using clinical research forms (CRFs) followed by entry into the Research Electronic Data Capture (REDCap) database. Research coordinators should verify all

demographic and health history to the participant's medical records prior to entry into REDCap. REDCap is a secure, web-based application designed to support data capture for research studies.[32] REDCap provides: 1) secured interface for validated data entry, 2) audit trails for tracking data manipulations and data storage and export procedures, 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for importing data from external sources. The University of Colorado Denver Informational Technology (IT) department will provide the host services for the REDCap secure application. Data extracted from the database for analysis will de-identified and linked to the original source using only a coded study number. All analysis will be conducted using SPSS statistical software program. UCD will serve as the coordinating site for all participating research sites. Data intake at all locations will be inputted directly into the lead REDCap database and all data analysis will be conducted by research personnel at UCD. REDCap survey privileges will be restricted to the non-affiliated locations for data entry only.

Study documents include study consent, CRFs, and study diaries. A study file should be constructed for each participant for maintaining these documents. All paper records will be securely stored in the locked research offices with limited access. Study databases will be stored on secure computers of the research team and backed by the secured server of the University of Colorado Denver.

Data sources will not be shared with outside institutions. Non-affiliated institutions participating in this study will only have access to the study resources for data entry. Any final study results presented to the non-affiliated sites will be de-identified. Data shared among the researchers will be sent in encrypted email messages. All data will be maintained until completion of study and properly stored per federal regulations after completion of study analysis. Any data remaining on research electronic devices (recording devices, computers hard drives) will be properly destroyed with the assistance of the University IT department.

All research sites will be responsible for maintaining a subject log with the subjects name and study ID number so that the patient's name is not entered into the database maintained at the host site. The study ID will serve as a link for participant and study data and will be used for data verification. This will be done to maintain patient confidentiality.

The Primary Investigator will be responsible for monitoring the study for unanticipated problems (i.e. breach of confidentiality) and reporting them to lead and local IRBs as appropriate.

10.2 Medical Monitoring

Medical monitoring and monitoring of SAEs across all sites will be monitored by Dr. Saketh Guntupalli on a continuous basis. All SAEs must be reported to Dr. Guntupalli at the University of Colorado within 48 hours of event. The sponsoring site will be responsible for reporting such events to the overseeing IRB within 5 days of event. Interim analysis will be done with data from all sites after 4 months of enrollment to examine any increased risk of SAEs as expected from standard of care.

10.3 Interim Analysis

Interim analysis will be conducted after the first 120 patients randomized to treatment (~60 per study arm, expected # at 4 months) will have completed participation. Study will be discontinued if one of the following is met:

- Significantly greater number of major bleeding (primary endpoint) or SAE/AEs in the investigational arm (apixaban) at the 5% level (alpha <0.05), or
- No Bleeding and no VTE events in study population and >90% adherence in investigational arm and >99% adherence in control arm.

10.4 Data Safety Monitoring Plan

The Principal Investigator (PI) will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial, executing the DSM plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (CU Cancer Center). The DSMC is responsible for ensuring data quality and patient safety for all clinical studies at the CU Cancer Center. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs), unanticipated problems (UAPs) and reportable adverse events (AEs)
- Has the authority to close and/or suspend trials for safety or trial conduct issues
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the CU Cancer Center Institutional DSM Plan, SAEs, UAPs and reportable AEs are reported to the DSMC, IRB and the sponsor per study protocol. All SAEs, UAPs and reportable AEs are to be reported to the DSMC within 5 business days of receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the Investigators and Clinical Research Coordinators (CRCs) at regularly scheduled disease-oriented working group meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The PI will provide a DSM report to the CU Cancer Center DSMC on a six month basis. The DSM report will include a protocol summary; current enrollment numbers; summary of toxicity data to include specific SAEs, UAPs and AEs; any dose modifications; all protocol deviations; and protocol amendments. The DSM report to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted, as well as any internal DSMB reports. Results and recommendations from the review of this six month report by the DSMC will then need to be submitted by the site to the IRB of record at the time of continuing review.

The coordinating site (UCD) is responsible for organizing and conducting monthly teleconferences with all participating sites. The PI will also be responsible for including data from all of the participating sites within the overall trial's six month DSM report to the DSMC to include minutes from monthly PI teleconferences. The Clinical Trials Office at UCD will provide monitoring of the coordinating site. The data manger will provide additional internal data validation for the coordinating site and monitoring for all additional participating sires. Each participating site will be responsible for submitting the results and recommendations from the DSMC's six month review to their IRB of record at the time of continuing review.

11. STATISTICAL CONSIDERATIONS

Data will be abstracted regarding participant demographics, surgical type, and length of hospital stay and development of DVT/PE. This is a comparative study designed to assess the safety with use of prophylactic anticoagulation following gynecologic cancer surgery using oral apixaban as compared to SQ enoxaparin. Secondary endpoints will assess the efficacy and adherence of oral apixaban as compared to SQ enoxaparin Compliance will be assessed with a margin of equivalence is set at 10% with a significance of $p< 0.05$.

Treatment will be taken for 28 consecutive days with follow-up continuing to 90 days. Bleeding events, symptoms for VTE and DVT or PE outcomes will be assessed during the treatment period. Additionally, participant adherence, satisfaction, and QOL will be measured at intervals during the treatment period. Risk for major bleeding and VTE event will be compared for apixaban versus the enoxaparin (control) arm. Participants will be analyzed employing a modified intention-to-treat approach (analyzed based on receiving assigned study medication at least once).

11.1 Sample Size

Previous studies have shown incidence of major bleeding at ~5% for the current standard of care (enoxaparin) versus an average of 3.5% risk of major bleeding for apixaban treatment. [19-21] For this safety evaluation of apixaban compared to enoxaparin, we expect with a sample size of 200 per arm to detect a difference between the treatment groups at a rate of 2% in one arm and 8% in the second arm at an alpha=0.05 and power of 80%.

11.2 Population for Analysis

A modified intent-to-treat analysis will be based on participants initiating assigned medication for first day of treatment. All participants randomized who receive the assigned study medication at least once will be included for analysis.

11.3 Primary Endpoint

The primary endpoint for the study is a major bleeding event *(Fatal bleeding, bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome, bleeding causing a fall in hemoglobin level of 20 g L^{-1} (1.24 mmol L^{-1}) or more, or leading to transfusion of two or more units of whole blood or red cell* [29]). This should also include clinically relevant non-major (CRNM) bleeding events that don't meet the definition of major bleeding but are associated with medical intervention, unscheduled contact with a physician, temporary cessation of drug therapy, or any other discomfort such as pain or impairment of activities of daily life.

Major Bleeding and CRNM bleeding event will be assessed by identification of clinical events (i.e. emergency room visit, hospital admission). Clinical events (i.e. emergency room visit, hospital admission) will be evaluated for major bleeding outcomes and verified with clinical and laboratory data by a blinded clinician. Assessment of major and CRNM bleeding events will be used to determine safety of apixaban as compared to enoxaparin, in the setting of gynecologic surgery. Risk analysis and time-to-event analysis will be conducted for the primary endpoint.

11.4 Secondary Endpoints

The secondary endpoints for this study are as follows:

11.4.1 VTE event *(DVT or PE outcome)*

VTE event *(DVT or PE outcome)* will be assessed by physical assessment for bleeding (DVT of PE), followed by confirmatory tests if suspected. All hospitalizations events in the

28-days post surgery will also be evaluated for VTE outcomes. Any confirmed DVT or PE will be recorded and study medication will be discontinued at that time. The rate of VTE events and the rates of VTE events causing hospitalizations will be compared between the apixaban versus the enoxaparin (control) arm. Risk analysis and time-to-event analysis will be conducted for this endpoint.

11.4.2 Adherence

Equivalence between the two treatment groups in terms of adherence to study medication will be investigated. Adherence will be collected in two ways: via counting unused medications in returned medication bottles/syringes and via information collected in subjects' diaries. Information collected via counting unused medications will be used as the endpoint for investigating equivalence adherence. Information collected in subjects' diaries will be used to investigate equivalence and verify information collected via unused medication. Compliance will be indicated by an adherence rate of 93%, or not greater than 2 missed days of medication) If participants, miss more than two days of medication, we will re-contact them, over the phone or in clinic, to further follow up on why they were non-compliance. This could be after the 90 day follow up.

11.4.3 Satisfaction

Satisfaction will be measured using participant questionnaire obtained at End of Treatment. Data will be analyzed qualitatively and quantitatively to describe common ease and complaints associated with use of each treatment regimen.

11.4.4 Quality of Life

Quality of Life (QOL) will be measured using the validated SF-8 instrument, QOL will be collected both at the enrollment visit and the end of treatment visit. Both intra and inter analysis will be conducted to examine changes in QOL after treatment and compare differences between the two treatment arms in QOL outcomes.

11.5 Statistical Analyses

Descriptive statistics using means, frequencies, and percentages will be computed to describe the study population. Participant data will be analyzed employing the intention-to-treat approach. Student's t-tests (for continuous variables) and chi-square tests (for categorical variables) will be used to compare the two groups for demographic, reproductive, and secondary outcome variables. For the primary outcome measure, major bleeding, and the secondary outcome, VTE event,,survival analysis such as a Kaplain Meyer curve will be used to compare survival curves for these outcomes. Logistic regression models will be used to identify significant independent predictors associated with the primary outcomes. A p value of <0.05 will be used to demonstrate statistical significance. IBM SPSS version 22 will be used for all statistical analyses.

12. STUDY MANAGEMENT

12.1 Compliance with the Protocol

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be reviewed by BMS. The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining IRB/IEC approval/favorable opinion, as soon as possible the deviation or change will be submitted to:

- IRB/IEC for review and approval/favorable opinion
- Regulatory Authority(ies), if required by local regulations

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to BMS.
If an amendment substantially alters the study design or increases the potential risk to the subject: (1) the consent form must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from subjects currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new subjects prior to enrollment.
If the revision is an administrative letter, investigators must inform their IRB(s)/IEC(s).

Regulatory coordination will be conducted by the division regulatory manager. It is the responsibility of the PI and the research team to submit all deviations. amendments, and SAEs/AE to the regulatory manager for submission to the IRB. The regulatory manager will be available for all monitoring visits and audits to address any issues.

12.1.1 Protocol Deviations

Deviations from the protocol, noted during site monitoring or review of study documents, should be recorded and maintained in site regulatory files. Local IRBs may request submission or protocol deviations at continuing review.

12.1.2 Protocol Amendments

Any amendments to the protocol will be first reviewed by BMS and then submitted to the IRB of the lead site for approval. Sub-sites will then be required to submit the protocol amendment to their local IRB and maintain all submission and approvals in their regulatory files. Sites should not initiate any changes to study procedures until after approval of the protocol amendment by their local IRB. Insignificant changes (i.e. personnel changes) may not have to be submitted to the sponsor and/or lead site first.

12.1.3 Subject Withdrawals

Subjects withdrawn from the study will not be replaced. All efforts should be made to conduct an end of treatment visit for return of study medications and VTE assessment. All participant documentation up until study withdrawal will be maintained and used for data analysis. In the event a participant is lost to follow-up, 3 documented attempts should be made to contact the participant to conduct an end of treatment visit. If after 3 attempts, the participant still does not return, a certified letter noting withdraw from study should be sent to the participant. The study coordinator will maintain a return receipt for such. Additionally, the study coordinator should send a self-addressed package to the participant for return of any study medications and/or study documents.

12.1.4 Medication Errors

In the event a participant is distributed the wrong study medication, the lead site should be notified immediately. If the participant only received the medication distributed in error, the treatment assignment will be adjusted to reflect the treatment arm for medication received. If the participant received the wrong medication after initial assignment and receiving initial dosing of the correct medication, please contact the medical monitor with instruction on how to proceed.

12.1.5 Participant Confidentiality

Data obtained during conduct of this study is to remain confidential and private. Participant confidentiality must be obtained in accordance to regulations set forth by Good Clinical Practice and HIPAA. Release of study data should only be done through the publication/presentation of results, lead by the Principal Investigator (PI). Study sites should not release any confidential data or findings of this study without the consent of the PI and the study sponsor.

12.1.6 Clinical Monitoring

Clinical monitoring of the study will be conducted by research personnel (data manager) from the University of Colorado Denver for all additional sites. The University of Colorado will conduct their own audit and validation of study entry with internal research personnel through the Clinical Trials office. In order to conduct monitoring, study sites should make staff and resources available for the following:

- Initial in-service of the study site, including investigator training and site tour
- Regular attendance of progress meetings
- Research staff available for interim monitoring visits
- All study documents (consents, CRFs, etc…) available for site visits in which the monitor will verify accuracy of data as entered into the electronic database
- Response to data requests via fax/email if site visit is not necessitated
- Maintenance of all regulatory documents and accessible for monitor review (UCD may request these be sent to the lead site for regulatory maintenance)
- Research staff available to response to data queries and resolve inconsistencies in study records
- Close out of the study at the study site

The study monitor will provide each site with a report of the monitor visit to be submitted to their local IRB. In addition to monitoring visits, a monthly conference call will take place among all sites to discuss treatment outcomes, enrollment, significant toxicities, dose modifications and responses. These meetings will be documents and the minutes shared with all sites.

Additionally, the University of Colorado DSMC and/or the study sponsor may request a site audit to evaluate conduct and compliance of the investigational protocol as a study site. All study documents and regulatory documents must be available to audit. The audit reviewer will also require direct access to study source (participant medical records relating to study) and time with the site investigator and/or regulatory personnel during their visit.

12.2 Records Retention

FDA law and regulations require the collection and maintenance of complete clinical study data. This includes information on subjects who withdraw from a clinical investigation, whether the subject decides to discontinue participation in the clinical trial (21 CFR 50.25(a)) or is discontinued by the investigator because the subject no longer qualifies under the protocol (for example, due to a significant adverse event or due to failure to cooperate with study requirements). FDA recognizes that a subject may withdraw from a study; however, the withdrawal does not extend to the data already obtained during the time the subject was enrolled. FDA's longstanding policy has been that all data collected up to the point of

withdrawal must be maintained in the database and included in subsequent analyses, as appropriate.

All study documentation should remain on study site in a secured area with limited access. The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS, whichever is longer.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed upon designee (eg, another investigator, IRB). Notice of such transfer will be given in writing to BMS.

12.2.1 Research Electronic Data Capture

All study data should be entered in the electronic data capture. For this study the electronic data capture will be supported by REDCap. Prior to the start of trial, site investigators and research staff must complete REDCap in-service provided by the University of Colorado Denver. The study site will maintain documentation of REDCap training for each person approved for accessing REDCap. Access will then be granted by the University of Colorado. Site personnel with REDCap access will be able to maintain study records with review and edit permission.

12.2.2. Data Management

All data entered into the REDCap database will be maintained by the host site for the REDCap database, the University of Colorado Denver. The University of Colorado research staff will review the database for completion of data and data inconsistencies and request resolution by the appropriate site. The University of Colorado will be responsible for all export and analysis of study data. Any requests for data sharing will be considered after completion of study analysis.

12.2.3 Confidentiality and Reporting of Results

The information on individual subjects arising from this study is to be considered confidential and transmitted to the sponsor only in a form that will not permit identification of the individual. The information obtained from the subjects that can be identified with the subject will remain confidential within the research team. Research teams will maintain all records in a secure area with limited access. Regulatory and sponsoring agencies may request access to the study records and related medical records of each participating subject. If requested, the subject's identity will remain confidential to the extent permitted by the applicable laws and regulations. The results of the research will be released to public agencies including regulatory agencies, clinical investigators, and research organizations without reference to items identifiable to a particular subject. The results will be published such that the identity of the subjects will not be disclosed and cannot be ascertained.

12.2.4 Study Drug Records

It is the responsibility of the investigator to ensure that a current disposition record of investigational product (those supplied by the BMS)is maintained at each study site where study drug and non-investigational product(s) is/are inventoried and dispensed. Records or logs must comply with applicable regulations and guidelines and should include:

- amount received and placed in storage area
- amount currently in storage area
- label ID number or batch number

- amount dispensed to and returned by each subject, including unique subject identifiers
- amount transferred to another area/site for dispensing or storage
- non-study disposition (eg, lost, wasted)
- amount destroyed at study site, if applicable
- amount returned to the BMS
- retain samples for bioavailability/bioequivalence, if applicable
- dates and initials of person responsible for Investigational Product (IP) dispensing/accountability, as per the Delegation of Authority Form.

12.2.5 Retention of Data

The clinical research records must be retained for a minimum of two years after the marketing application is approved for the drug for the indication for which it was being investigated. Alternatively, if no application will be filed or if the application is not approved for the requested indication, the records must be retained for a minimum of two years after the investigation is discontinued and FDA is notified. 21 CFR §312.62(c)

12.3 Destruction of Investigational Product

If the study drugs are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures. Appropriate records of the disposal must be maintained.

12.4 Conflict of Interest

Investigators will be affiliated with their study sites and have no affiliation with BMS. They will receive support for this clinical trial from the Bristol-Meyers Squibb, but will not profit from results, either positive or negative, with regard to the product being evaluated. Bristol-Meyers Squibb could profit from the successful development of this product.

12.5 Publication Policy

Data on the use of the study medication and results of all clinical study are considered confidential. UCD will lead any publication of the results of the study. Any publications or presentations that result from this study will maintain confidentiality of study participants. Bristol-Meyers Squibb (BMS) owns all proprietary information about the investigational drug. BMS will be consulted on all proposed publications, papers, abstracts, manuscripts, posters or other written materials which include data relating to the study or the use of study drug supplied by BMS.

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Appendix 1: VTE Assessment Clinical Research Form

VTE Assessment CRF (Using Wells' Criteria Score)

Is participant complaining of suspected DVT/PE symptoms?

If Yes, Indicate location of suspected VTE? Left Leg Right Leg Both Legs
Chest

DVT Assessment
Please score the following physical assessment of DVT symptoms

Subject Assessment	**Present**		**Score**
Active Cancer	Yes +1	No +0	
Bedridden recently >3 days or major surgery within 4 weeks	Yes +1	No +0	
Calf swelling >3cm compared to the other leg	Yes +1	No +0	
Collateral (non-varicose) superficial veins present	Yes +1	No +0	
Entire leg swollen	Yes +1	No +0	
Localized tenderness along deep venous system	Yes +1	No +0	
Pitting edema, greater in the symptomatic leg	Yes +1	No +0	
Paralysis, paresis, or recent plaster immobilization of the lower extremity	Yes +1	No +0	
Previously documented DVT	Yes +1	No +0	
Alternative diagnosis to DVT as likely or more likely	Yes -2	No +0	
Total Score			

Score 0 or less: LOW RISK; 1-2: MODERATE RISK; 3 or higher: HIGH RISK

Assessment of DVT conducted by (initials): _____

Did subject meet HIGH risk probability? Yes No

For subjects meeting HIGH risk, confirm suspicion with ULTRASOUND

Did subject complete ULTRASOUND? Yes No
Date of ultrasound _____

ULTRASOUND RESULTS:
DVT is: NOT PRESENT PROBABLE
CONFIRMED

PE Assessment

Heart rate _____bpm

Is the subject experiencing any of the following:

Heart rate greater than 100bpm? Yes No

Hemoptysis (coughing up blood)? Yes No

Assessment of PE conducted by (initials): _____

Did subject meet either criteria for PE probability? Yes No

Subjects meeting any of the above should confirm PE suspicion with CHEST CT

Did subject complete Chest CT? Yes No
Date of ultrasound _____

CHEST CT RESULTS:
PE is: NOT PRESENT PROBABLE CONFIRMED

Was subject discontinued from study Yes No
(For probable or confirmed VTE, if yes, complete End of Treatment and Discontinuation forms)

Completed By: _____ (Initials)

Appendix 2: Satisfaction Questionnaire

Subject Satisfaction
Please rate your answers using the scale provided.

Was the medication easy to take?

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

Did you have difficulty remembering to take your medication?

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

Did you have pain associated with taking the medication?

Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree

Appendix 3: Quality of Life Health Survey

This survey asks you about your health in the last 4 weeks. Please indicate the best response for each of the following health assessments.

SF-8 Health Survey

1. Overall, how would you rate your health **in the past 4 weeks**?

   ☐ Excellent ☐ Very good ☐ Good ☐ Fair ☐ Poor ☐ Very poor

2. **In the past 4 weeks**, how much did physical health problems limit your usual physical activities (such as walking or climbing stairs)?

   ☐ Not at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do physical activities

3. **In the past 4 weeks**, how much difficulty did you have doing your daily work, both at home and away from home, because of your physical health?

   ☐ None at all ☐ A little bit ☐ Some ☐ Quite a lot ☐ Could not do daily work

4. How much bodily pain have you had **in the past 4 weeks**?

   ☐ None ☐ Very mild ☐ Mild ☐ Moderate ☐ Severe ☐ Very severe

5. **In the past 4 weeks**, how much energy did you have?

   ☐ Very Much ☐ Quite a lot ☐ Some ☐ A little ☐ None

6. **In the past 4 weeks**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

   ☐ Not at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do social activities

7. **In the past 4 weeks**, how much have you been bothered by emotional problems (such as feeling anxious, depressed or irritable)?

   ☐ Not at all ☐ Slightly ☐ Moderately ☐ Quite a lot ☐ Extremely

8. **In the past 4 weeks**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

☐ Not at all ☐ Very little ☐ Somewhat ☐ Quite a lot ☐ Could not do daily activities

Appendix 4: Study Visit Clinical Research Forms

Appendix 4.1 Screening Visit CRF

Did subject sign informed consent? Yes No

Date of informed consent _____

Date of Birth: _____ Age: _____

Race/Ethnicity:

- ☐ White, non-Hispanic
- ☐ White, Hispanic/Latin origin
- ☐ American Indian or Alaskan Native
- ☐ Asian
- ☐ Black or African American
- ☐ Native Hawaiian or Pacific Islander
- ☐ Other _____

Menopause Status:

- ☐ Pre-menopause
- ☐ Post-menopause

Does subject have suspected or confirmed cancer malignancy?
Yes No

Is subject suitable candidate for surgery (meets appropriate performance status, no significant cardiac/renal/hepatic dysfunction)? Yes No

Completed By: _____ (Initials)

If yes, proceed with additional screening criteria. If no, subject is not eligible.

Subject Assessment	**Exclusion Met**	
Malignancy or mass that is non-gynecologic in origin (mass/tumor of origin other than reproductive organ such as rectal, abdominal, breast)	Yes	No
Known history of VTE prior to diagnosis (DVT or PE) due to increased underlying risk of new event	Yes	No
Concomitant NSAIDS or other anticoagulant/antiplatelet therapy, including ASA >81mg/day	Yes	No
SSIRs, or SNIRs (common anti-depressant therapies)	Yes	No
Uncontrolled Severe Hypertension (Systolic >200mmHg or Diastolic > 120mmhg)	Yes	No
Positive pregnancy test (pre-menopausal women) on day of surgery	Yes	No
Active bleeding condition (not limited to: thrombocytopenia, haemophilias, potential bleeding lesions, recent trauma or surgery, recent stroke, confirmed intracranial or intraspinal bleeding)	Yes	No
Known or documented bleeding disorders not limited to: anti-phospholipid syndrome, homozygotes for Factor V Leiden deficiency, antithrombin III deficiency, protein C deficiency, Protein S deficiency, hyperhomocystenemia, systemic lupus erythematous, or Prothrombin G2020 gene mutation,	Yes	No
Significant renal disease as defined by creatinine clearance less than 30 mL/min *[[140 - age(yr)]*weight(kg)]/[72*serum Cr(mg/dL)] *(multiply by 0.85 for women)*	Yes	No
Significant liver disease as defined as AST or ALT twice than normal	Yes	No
Has prosthetic heart valve	Yes	No
Concomitant use of dual strong inhibitors or inducers (CYP3A4, P-gp)	Yes	No
Protein C deficiency	Yes	No
Documented allergy to apixaban and/or enoxaparin	Yes	No
Deemed otherwise clinically unfit for clinical trial per Investigator's discretion	Yes	No
Does subject meet any of the above exclusions?	**Yes**	**No**

If yes, subject is not eligible for study. Please log as a screen-fail

Investigator review of subject eligibility

_____ Date_____

Signature

Appendix 4.2 Visit 1 (pre-op) CRF

Was visit conducted? Yes No

Was visit conducted 1-30 days prior to scheduled surgery? Yes No
If no, complete deviation log for visit outside window

Physical Assessment		
Blood Pressure		
Pulse		
Temperature		
Respiratory rate		
Height		
Weight		
Calculate BMI $\frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$		
Review of Systems		
Head and Neck	Normal	Abnormal
Cardiovascular	Normal	Abnormal
Pulmonary/Chest	Normal	Abnormal
Abdomen	Normal	Abnormal
Gastrointestinal	Normal	Abnormal
Genitourinary	Normal	Abnormal
Musculoskeletal	Normal	Abnormal
Lymphadenopathy	Normal	Abnormal
Skin	Normal	Abnormal
Neurological	Normal	Abnormal
Hematological	Normal	Abnormal
Psychiatric	Normal	Abnormal
Overall Physical assessment	**Normal**	**Abnormal**

Assessment recorded by: _____ (Initials)

Does the subject have known Diabetes? Yes No

Does the subject have known Hypertension? Yes No

Other Medical Conditions: _____

_____

Medications: _____

_____

Allergies: _____

Cancer Diagnosis

Suspected/Confirmed Malignancy Origin:

☐ Uterine/Endometrial

☐ Ovarian

☐ Cervical

☐ Other _____

Please have subject complete QOL CRF for V0

Completed By: _____ (Initials)

Appendix 4.3 Surgery Visit CRF
Date of Surgery: _____

Surgical Intervention

☐ Minimally Invasive/Robotic

☐ Open Surgery

Indicate all surgical procedures conducted:

☐ TAH
☐ TAH with BSO/USO
☐ BSO/USO
☐ Radical Hysterectomy
☐ Lymph node Dissection
☐ Bowel resection
☐ Removal of Omentum
☐ Other: _____

For women of childbearing potential, was a serum or urine pregnancy test conducted prior to surgery with NEGATIVE results? Yes No N/A

Did subject receive compression devices prior to surgery? Yes No

Did subject receive heparin subQ prior to surgery? Yes No

Was heparin continued thru surgery? Yes No

Was heparin provided TID starting 6-8 hours following surgery until randomization? Yes No
(If subject stopped heparin > 24 hours prior to randomization, subject may be at additional risk for VTE event)

Was there any complicated events during/immediately following surgery?

Yes No

If yes, describe: _____

Surgery Length: Start/cut time (HH:MM) _____
End/close time (HH:MM) _____

Does subject continue to meet criteria for randomization? Yes No

Subject to be randomized 1-7 days following surgery. Study medication should administered on study day 1 following surgery (after stop of heparin therapy and epideral).

For WOCBP, they must not be breastfeeding and must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug plus 5 half-lives of study drug apixiban (2.5 days) plus 30 days (duration of ovulatory cycle) for a total of 32.5 days post-treatment completion unless hysterectomy was performed.

Completed By: _____ (Initials)

Appendix 4.4 Visit 2 (Randomization) CRF

Date of Randomization: _____

Has subject experienced a major bleeding or CRNM event since surgery?
Yes No

If yes, indicate:

Bleeding event: _____

Date Bleeding event: _____

Has subject experienced a VTE event since surgery? Yes No

If yes, indicate:

VTE event type: _____

Date VTE event: _____

Medication prescribe _____

Verified events in EMR conducted by: _____

If subject has experienced bleeding/VTE since surgery or does not continue to meet eligibility criteria, do not RANDOMIZE subject and discontinue enrollment.

Treatment Arm:

☐ Apixaban 2.5 mg BID

☐ Enoxaparin 40 mg sq QD

Did subject receive 28-day supply of study medication? Yes No

Did subject receive education for taking medication? Yes No

Did subject receive education for storing medication? Yes No

Did subject receive study diaries? Yes No

Did subject receive education for completing diaries? Yes No

Date to start medication: _____

Was subject scheduled for V2 (2 weeks post-op +/- 2 days) Yes No

Subject to take medication:

- **Starting on day 2 following surgery**
- **Apixaban 2x day OR Enoxaparin 1x day, for 28 days (study days 1-28)**
- **Record time take medication in subject diary**

Completed By: _____ (Initials)

Appendix 4.5 Visit 3 (post-op) CRF

Was visit conducted? Yes No

Was visit conducted 14 days post-op (+/- 4 days)? Yes No
If no, complete deviation log for visit outside window (unless early discontinuation)

Vitals	
Blood Pressure	
Pulse	
Temperature	
Respiratory rate	
Height	
Weight	
Calculate BMI : Weight (kg) / (Height (m))^2	

Confirm Subject Cancer diagnosis (based on final pathology):

Malignancy is: ☐BENIGN ☐BORDERLINE ☐MALIGNANT

Diagnosis Origin:

☐Uterine/Endometrial

☐Ovarian

☐Cervical

☐Other _____

Stage

☐I___ ☐II___ ☐III___ ☐IV___

Recorded by: _____ (initials)

Is subject meeting standard post-op milestones? Yes No

Has subject been hospitalized or to the emergency department since discharge?
Yes No

Has subject experienced a major bleeding or CRNM event since last visit?
Yes No

If yes, indicate

Bleeding event: _____

Date Bleeding event: _____

Has subject experienced a VTE event since last visit? Yes No

If yes, indicate:

VTE event type: _____

Date VTE event: _____

Medication prescribed _____

Does subject complain of any pain in legs or chest? Yes No

Was assessment of VTE conducted Yes No
If Yes, Complete VTE CRF

If subject reported a major bleeding of VTE event, discontinue study and complete discontinuation CRF.

Medication Adherence (applicable if subject discontinued study treatment)
Did subject return Medication Bottles/syringes? Yes No N/A

Total UNUSED returned _____ (# days unused out of 28 days)

Did subject meet medication compliance per bottle/syringe indication? (not > 2 days UNUSED)
Yes No N/A

Did Subject return Subject Diaries for review? Yes No N/A

Did subject meet medication compliance per diary? (not > 2 days of missed medication)

Yes No N/A

Schedule subject to return at day 28 (+/- 4 days). Instruct subject to return all medication and dairies at that time.

AE and Medical Adherence Completed By: _____ (Initials)

Appendix 4.6 Visit 4 (End of Treatment/28 days) CRF

Was visit conducted? Yes No

Was visit conducted 28 days from V1 (+/- 4 days)? Yes No
If no, complete deviation log for visit outside window (unless early discontinuation)

Was subject discontinued early from study? Yes No

Physical Assessment		
Blood Pressure		
Pulse		
Temperature		
Respiratory rate		
Height		
Weight		
Calculate BMI $\frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$		
Review of Systems		
Head and Neck	Normal	Abnormal
Cardiovascular	Normal	Abnormal
Pulmonary/Chest	Normal	Abnormal
Abdomen	Normal	Abnormal
Gastrointestinal	Normal	Abnormal
Genitourinary	Normal	Abnormal
Musculoskeletal	Normal	Abnormal
Lymphadenopathy	Normal	Abnormal
Skin	Normal	Abnormal
Neurological	Normal	Abnormal
Hematological	Normal	Abnormal
Psychiatric	Normal	Abnormal
Overall Physical assessment	**Normal**	**Abnormal**

Did subject physical health change from baseline? Yes No

Recorded by: _____ (initials)

Bleeding/VTE assessment

Has subject been hospitalized or to the emergency department since last visit?
Yes No

Has subject experienced a major bleeding or CRNM event since last visit?
Yes No

If yes, indicate:
Bleeding event: _____

Date Bleeding event: _____

Has subject experienced a VTE event since last visit? Yes No

If yes, indicate:
VTE event type: _____

Date VTE event: _____

Medication prescribed: _____

Does subject complain of any pain in legs or chest? Yes No

Was assessment of VTE conducted Yes No
If Yes, Complete VTE CRF

If subject reported a major bleeding of VTE event, discontinue study and complete discontinuation CRF.

Was QOL assessment conducted? Yes No
Have subject complete QOL

Was Satisfaction assessment conducted? Yes No
Have subject complete satisfaction

Medication Adherence

Did subject return Medication Bottles/syringes(?)? Yes No

Total UNUSED returned _____ (# days unused out of 28 days)

Pills only: # expected returned: 4 pills # pills returned total: _____

Did subject meet medication compliance per bottle/syringe indication? (not > 2 days UNUSED)

Yes No

Did Subject return Subject Diaries? Yes No

Did subject meet medication compliance per diary? (not > 2 days of missed medication)

Yes No

AE and Medical Adherence Completed By: _____ (Initials)

Visit 4.7 Visit 5 (Follow-up/90 days) CRF

Was visit conducted? Yes No

Was visit conducted 90 days post-op (+/- 14 days)? Yes No

If no, complete deviation log for visit outside window (unless early discontinuation)

Vitals	
Blood Pressure	
Pulse	
Temperature	
Respiratory rate	
Height	
Weight	
Calculate BMI : Weight (kg) / (Height (m))^2	

Recorded by: _____ (initials)

Is subject meeting standard post-op milestones? Yes No

Has subject been hospitalized or to the emergency department since last visit? Yes No

Has subject experienced a major bleeding or CRNM event since last visit? Yes No

If yes, indicate:

Bleeding event: _____

Date Bleeding event: _____

Has subject experienced a VTE event since last visit? Yes No

If yes, indicate:

VTE event type: _____

Date VTE event: _____

Medication prescribed: _____

Does subject complain of any pain in legs or chest? Yes No

Was assessment of VTE conducted? Yes No

If Yes, Complete VTE CRF

AR assessment completed By: _____
(Initials)

Subject has completed participation in study.

_____ Date: _____
Investigator signature

Visit 4.8 Unanticipated Event Visit CRF

Reason for UAE: _____
(report AEs per protocol)

Vitals	
Blood Pressure	
Pulse	
Temperature	
Respiratory rate	
Height	
Weight	
Calculate BMI $\frac{\text{Weight (kg)}}{(\text{Height (m)})^2}$	

Recorded by: _____ (initials)

Has subject been hospitalized or to the emergency department since last visit?
Yes No

Has subject experienced a major bleeding or CRNM event since last visit?
Yes No

If yes, indicate:

Bleeding event: _____

Date Bleeding event: _____

Has subject experienced a VTE event since last visit? Yes No

If yes, indicate:

VTE event type: _____

Date VTE event: _____

Medication prescribed: _____

Does subject complain of any pain in legs or chest? Yes No

Was assessment of VTE conducted Yes No
If Yes, Complete VTE CRF

Was study medication stopped?
Yes No

If Yes, indicate: Date stopped: _____

Stopped by: ☐Investigator ☐Subject

If subject reported a major bleeding of VTE event, discontinue study and complete discontinuation CRF and V4 End of Treatment.

Was subject discontinued early from study? Yes No

AE assessment completed By: _____
(Initials)

Appendix 4.9 Early Discontinuation CRF

Reason for Early Discontinuation:

☐ Major Bleeding event

☐ VTE event

☐ Medication Non-Compliance

☐ Contradiction to Study Medication

☐ Lost to Follow-up/Withdrawal

☐ Death

☐ Investigator Discretion

☐ Other: _____

Date of study discontinuation: _____

Was study medication stopped? Yes No

If Yes, indicate: Date stopped: _____

Stopped by: ☐ Investigator ☐ Subject

Was End of Treatment (V4) conducted Yes No

Complete V4 CRF

Recorded by: _____ (Initials)

Subject has been discontinued from participation in study.

_____ Date: _____
Investigator signature

Appendix 5: Subject Diary

Study ID: **Study Initials:** **Site #:**

Subject Diary

Date	Study Day	Did you take your study medication today?	Time you took study medication	Time you took 2nd dose of medicaiton (PILLS ONLY)	Other Medications you took today	Reason for Other Medications	Complaints
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
		☐ Ys ☐ N ☐ NA	___:____ am pm ☐ did not take medication	___:____ am pm ☐ did not take medication			
						Reviewed by:	

Bristol-Meters Squibb Protocol CV185-394; COMIRB Protocol: 14-1574; Version 1.0 Date 30-Sep-2014

Appendix 6: Apixaban Investigator Brochure

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELIQUIS safely and effectively. See full prescribing information for ELIQUIS.

ELIQUIS® (apixaban) tablets for oral use

Initial U.S. Approval: 2012

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

See full prescribing information for complete boxed warning.

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS: Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. To reduce this risk, consider coverage with another anticoagulant if ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy. (2.5, 5.1, 14.1)

(B) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. (5.3)

– – – – – – – – – – – – – – – – RECENT MAJOR CHANGES – – – – – – – – – – – – – – – –

Boxed Warning	8/2014
Indications and Usage (1.2)	3/2014
Indications and Usage (1.3, 1.4, 1.5)	8/2014
Dosage and Administration (2.1)	8/2014
Dosage and Administration (2.8)	3/2014
Warnings and Precautions (5.1)	8/2014
Warnings and Precautions (5.3)	3/2014
Warnings and Precautions (5.5)	8/2014

– – – – – – – – – – – – – – – – – – INDICATIONS AND USAGE – – – – – – – – – – – – – – – – – –

ELIQUIS is a factor Xa inhibitor anticoagulant indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. (1.1)
- for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery. (1.2)
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following initial therapy. (1.3, 1.4, 1.5)

– – – – – – – – – – – – – – – DOSAGE AND ADMINISTRATION – – – – – – – – – – – – – – –

- Reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation:
  - The recommended dose is 5 mg orally twice daily. (2.1)
  - In patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, the recommended dose is 2.5 mg orally twice daily. (2.2)
- Prophylaxis of DVT following hip or knee replacement surgery:
  - The recommended dose is 2.5 mg orally twice daily. (2.1)
- Treatment of DVT and PE:
  - The recommended dose is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily. (2.1)
- Reduction in the risk of recurrent DVT and PE following initial therapy:
  - The recommended dose is 2.5 mg taken orally twice daily. (2.1)

– – – – – – – – – – – – – – DOSAGE FORMS AND STRENGTHS – – – – – – – – – – – – – –

- Tablets: 2.5 mg and 5 mg (3)

– – – – – – – – – – – – – – – – – CONTRAINDICATIONS – – – – – – – – – – – – – – – – –

- Active pathological bleeding (4)
- Severe hypersensitivity to ELIQUIS (apixaban) (4)

– – – – – – – – – – – – – – WARNINGS AND PRECAUTIONS – – – – – – – – – – – – – –

- ELIQUIS can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. (5.2)
- Prosthetic heart valves: ELIQUIS use not recommended. (5.4)

– – – – – – – – – – – – – – – – – ADVERSE REACTIONS – – – – – – – – – – – – – – – – –

Most common adverse reactions (>1%) are related to bleeding. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

– – – – – – – – – – – – – – – – – DRUG INTERACTIONS – – – – – – – – – – – – – – – – –

- Strong dual inhibitors of CYP3A4 and P-gp increase blood levels of apixaban. Reduce dose or avoid coadministration. (2.2, 7.1, 12.3)
- Simultaneous use of strong dual inducers of CYP3A4 and P-gp reduces blood levels of apixaban: Avoid concomitant use. (2.2, 7.2, 12.3)

– – – – – – – – – – – – – – USE IN SPECIFIC POPULATIONS – – – – – – – – – – – – – –

- *Pregnancy:* Not recommended. (8.1)
- *Nursing Mothers:* Discontinue drug or discontinue nursing. (8.3)
- *Severe Hepatic Impairment:* Not recommended. (12.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 8/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.5), Warnings and Precautions (5.1), and Clinical Studies (14.1)]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions (5.3)]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions (5.3)]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ELIQUIS® (apixaban) is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

1.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

1.3 Treatment of Deep Vein Thrombosis

ELIQUIS is indicated for the treatment of DVT.

1.4 Treatment of Pulmonary Embolism

ELIQUIS is indicated for the treatment of PE.

1.5 Reduction in the Risk of Recurrence of DVT and PE

ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose of ELIQUIS for most patients is 5 mg taken orally twice daily.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily. The initial dose should be taken 12 to 24 hours after surgery.

- In patients undergoing hip replacement surgery, the recommended duration of treatment is 35 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 12 days.

Treatment of DVT and PE

The recommended dose of ELIQUIS is 10 mg taken orally twice daily for 7 days, followed by 5 mg taken orally twice daily.

Reduction in the Risk of Recurrence of DVT and PE

The recommended dose of ELIQUIS is 2.5 mg taken orally twice daily after at least 6 months of treatment for DVT or PE *[see Clinical Studies (14.3)]*.

2.2 Dosage Adjustments

In patients with nonvalvular atrial fibrillation: The recommended dose of ELIQUIS is 2.5 mg twice daily in patients with any 2 of the following characteristics:

- age ≥80 years
- body weight ≤60 kg
- serum creatinine ≥1.5 mg/dL

Coadministration with strong dual CYP3A4 and P-gp inhibitors: For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, reduce the dose by 50% when ELIQUIS is coadministered with drugs that are strong dual inhibitors of cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) (e.g., ketoconazole, itraconazole, ritonavir, clarithromycin) *[see Clinical Pharmacology (12.3)]*.

In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with strong dual inhibitors of CYP3A4 and P-gp *[see Drug Interactions (7.1)]*.

2.3 Missed Dose

If a dose of ELIQUIS is not taken at the scheduled time, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

2.4 Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

2.5 Converting from or to ELIQUIS

Switching from warfarin to ELIQUIS: Warfarin should be discontinued and ELIQUIS started when the international normalized ratio (INR) is below 2.0.

Switching from ELIQUIS to warfarin: ELIQUIS affects INR, so that initial INR measurements during the transition to warfarin may not be useful for determining the appropriate dose of warfarin. If continuous anticoagulation is necessary, discontinue ELIQUIS and begin both a parenteral anticoagulant and warfarin at the time the next dose of ELIQUIS would have been taken, discontinuing the parenteral anticoagulant when INR reaches an acceptable range.

Switching between ELIQUIS and anticoagulants other than warfarin: Discontinue one being taken and begin the other at the next scheduled dose.

2.6 Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment.

Because patients with moderate hepatic impairment may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2)]*.

ELIQUIS is not recommended in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

2.7 Renal Impairment

The dosing adjustment for patients with moderate renal impairment and nonvalvular atrial fibrillation is described above *[see Dosage and Administration (2.2)]*. The recommended dose for nonvalvular atrial fibrillation patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age ≥80 years or body weight ≤60 kg) is present *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)]*.

No dose adjustment is required for the following indications:

- for the prophylaxis of DVT, which may lead to PE, in patients who have undergone hip or knee replacement surgery.
- for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE.

2.8 Administration Options

For patients who are unable to swallow whole tablets, 5 mg and 2.5 mg ELIQUIS tablets may be crushed and suspended in 60 mL D5W and immediately delivered through a nasogastric tube (NGT) *[see Clinical Pharmacology (12.3)]*. Information regarding the administration of crushed and suspended ELIQUIS tablets swallowed by mouth is not available.

3 DOSAGE FORMS AND STRENGTHS

- 2.5 mg, yellow, round, biconvex, film-coated tablets with "893" debossed on one side and "2½" on the other side.
- 5 mg, pink, oval-shaped, biconvex, film-coated tablets with "894" debossed on one side and "5" on the other side.

4 CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions (6.1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.5) and Clinical Studies (14.1)]*.

5.2 Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.2) and Adverse Reactions (6.1)]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions (7.3)]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

There is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. A specific antidote for ELIQUIS is not available. Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3)]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is neither scientific rationale for reversal nor experience with systemic hemostatics (desmopressin and aprotinin) in individuals receiving apixaban. Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage (10)]*.

5.3 Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel, or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

5.4 Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

5.5 Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased risk of thrombotic events after premature discontinuation *[see Warnings and Precautions (5.1)]*
- Bleeding *[see Warnings and Precautions (5.2)]*
- Spinal/epidural anesthesia or puncture *[see Warnings and Precautions (5.3)]*

ELIQUIS® (apixaban)

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14)]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per year) in ARISTOTLE and AVERROES.

Major bleeding was defined as clinically overt bleeding that was accompanied by one or more of the following: a decrease in hemoglobin of 2 g/dL or more; a transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or bleeding that was fatal. Intracranial hemorrhage included intracerebral (hemorrhagic stroke), subarachnoid, and subdural bleeds.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE

	ELIQUIS N=9088 n (%/year)	Warfarin N=9052 n (%/year)	Hazard Ratio (95% CI*)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Gastrointestinal (GI)‡	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Intracranial	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Intraocular§	32 (0.21)	22 (0.14)	1.42 (0.83, 2.45)	-
Fatal¶	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
CRNM**	318 (2.08)	444 (3.00)	0.70 (0.60, 0.80)	<0.0001

* Confidence interval.

† International Society on Thrombosis and Hemostasis (ISTH) major bleed assessed by sequential testing strategy for superiority designed to control the overall type I error in the trial.

‡ GI bleed includes upper GI, lower GI, and rectal bleeding.

§ Intraocular bleed is within the corpus of the eye (a conjunctival bleed is not an intraocular bleed).

¶ Fatal bleed is an adjudicated death because of bleeding during the treatment period and includes both fatal extracranial bleeds and fatal hemorrhagic stroke.

** CRNM = clinically relevant nonmajor bleeding.

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, ELIQUIS dose, type of atrial fibrillation (AF), and aspirin use at randomization (Figure 1). Subjects treated with apixaban with diabetes bled more (3.0% per year) than did subjects without diabetes (1.9% per year).

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

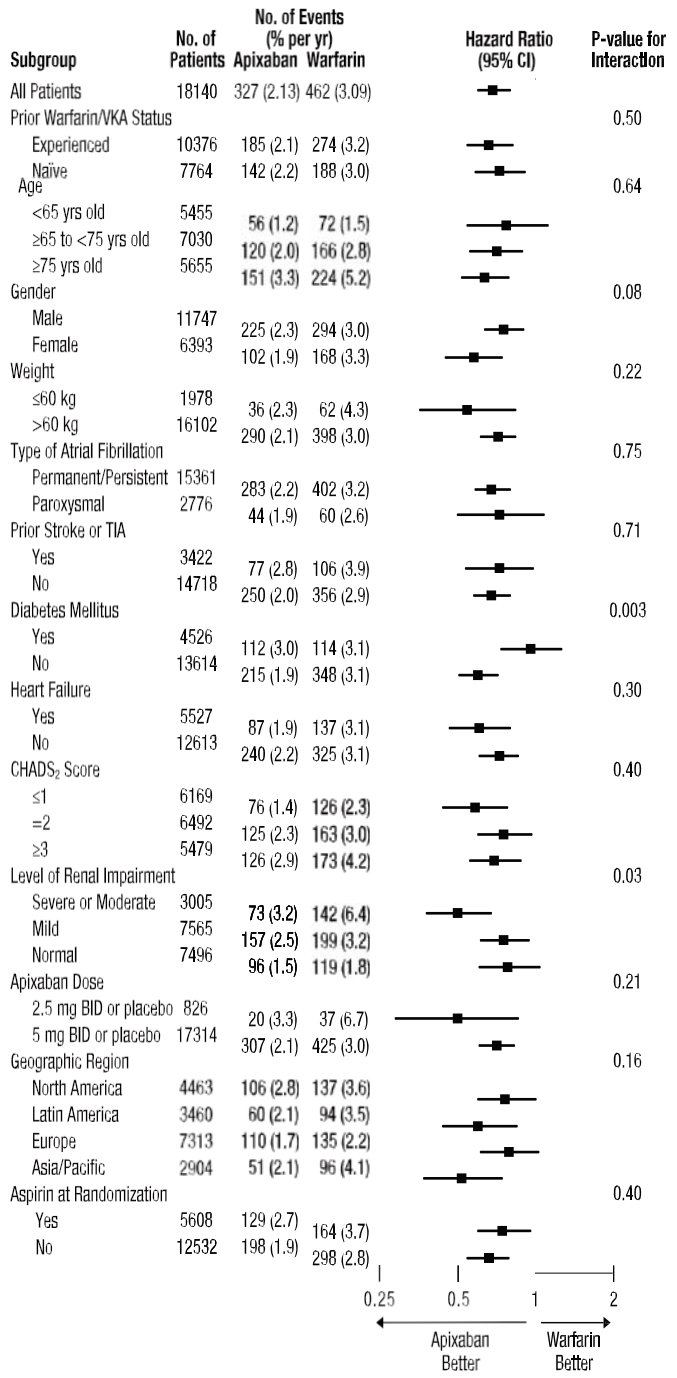

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.
† Includes 13 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of apixaban (administered 12 to 24 hours post surgery).
§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.
¶ CRNM = clinically relevant nonmajor.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture site hematoma and catheter site hemorrhage)	54 (0.9)	60 (1.0)

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Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery *(Continued)*

	ELIQUIS, n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

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Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg N=840 n (%)	ELIQUIS 5 mg N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg N=840 n (%)	ELIQUIS 5 mg N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae *Eye disorders:* conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

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ELIQUIS® (apixaban)

7 DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

7.1 Strong Dual Inhibitors of CYP3A4 and P-gp

For patients receiving ELIQUIS doses greater than 2.5 mg twice daily, the dose of ELIQUIS should be decreased by 50% when it is coadministered with drugs that are strong dual inhibitors of CYP3A4 and P-gp (e.g., ketoconazole, itraconazole, ritonavir, or clarithromycin) *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with strong dual inhibitors of CYP3A4 and P-gp *[see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)]*.

7.2 Strong Dual Inducers of CYP3A4 and P-gp

Avoid concomitant use of ELIQUIS with strong dual inducers of CYP3A4 and P-gp (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3)]*.

7.3 Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo. The rate of ISTH major bleeding was 2.77% per year with apixaban versus 0.62% per year with placebo in patients receiving single antiplatelet therapy and was 5.91% per year with apixaban versus 2.50% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and the bleeding risk on warfarin from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of ELIQUIS in pregnant women. Treatment is likely to increase the risk of hemorrhage during pregnancy and delivery. ELIQUIS should be used during pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.

Treatment of pregnant rats, rabbits, and mice after implantation until the end of gestation resulted in fetal exposure to apixaban, but was not associated with increased risk for fetal malformations or toxicity. No maternal or fetal deaths were attributed to bleeding. Increased incidence of maternal bleeding was observed in mice, rats, and rabbits at maternal exposures that were 19, 4, and 1 times, respectively, the human exposure of unbound drug, based on area under plasma-concentration time curve (AUC) comparisons at the maximum recommended human dose (MRHD) of 10 mg (5 mg twice daily).

8.2 Labor and Delivery

Safety and effectiveness of ELIQUIS during labor and delivery have not been studied in clinical trials. Consider the risks of bleeding and of stroke in using ELIQUIS in this setting *[see Warnings and Precautions (5.2)]*.

Treatment of pregnant rats from implantation (gestation Day 7) to weaning (lactation Day 21) with apixaban at a dose of 1000 mg/kg (about 5 times the human exposure based on unbound apixaban) did not result in death of offspring or death of mother rats during labor in association with uterine bleeding. However, increased incidence of maternal bleeding, primarily during gestation, occurred at apixaban doses of ≥25 mg/kg, a dose corresponding to ≥1.3 times the human exposure.

8.3 Nursing Mothers

It is unknown whether apixaban or its metabolites are excreted in human milk. Rats excrete apixaban in milk (12% of the maternal dose).

Women should be instructed either to discontinue breastfeeding or to discontinue ELIQUIS therapy, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 and older, and >31% were 75 and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 and older, while 16% were 75 and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 and older and >13% were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

8.6 End-Stage Renal Disease Patients Maintained with Hemodialysis

Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation for patients with nonvalvular atrial fibrillation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥80 years or body weight ≤60 kg, reduce dose to 2.5 mg twice daily *[see Dosage and Administration (2.7) and Clinical Pharmacology (12.2, 12.3)]*.

10 OVERDOSAGE

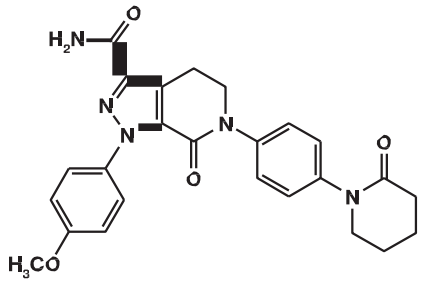
There is no antidote to ELIQUIS. Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions (5.2)]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of apixaban overdose or accidental ingestion.

11 DESCRIPTION

ELIQUIS (apixaban), a factor Xa (FXa) inhibitor, is chemically described as 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide. Its molecular formula is $C_{25}H_{25}N_5O_4$, which corresponds to a molecular weight of 459.5. Apixaban has the following structural formula:



Apixaban is a white to pale-yellow powder. At physiological pH (1.2–6.8), apixaban does not ionize; its aqueous solubility across the physiological pH range is ~0.04 mg/mL.

ELIQUIS tablets are available for oral administration in strengths of 2.5 mg and 5 mg of apixaban with the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Apixaban is a selective inhibitor of FXa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound FXa, and prothrombinase activity. Apixaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, apixaban decreases thrombin generation and thrombus development.

12.2 Pharmacodynamics

As a result of FXa inhibition, apixaban prolongs clotting tests such as prothrombin time (PT), INR, and activated partial thromboplastin time (aPTT). Changes observed in these clotting tests at the expected therapeutic dose, however, are small, subject to a high degree of variability, and not useful in monitoring the anticoagulation effect of apixaban.

The Rotachrom® Heparin chromogenic assay was used to measure the effect of apixaban on FXa activity in humans during the apixaban development program. A concentration-dependent increase in anti-FXa activity was observed in the dose range tested and was similar in healthy subjects and patients with AF.

This test is not recommended for assessing the anticoagulant effect of apixaban.

Pharmacodynamic Drug Interaction Studies

Pharmacodynamic drug interaction studies with aspirin, clopidogrel, aspirin and clopidogrel, prasugrel, enoxaparin, and naproxen were conducted. No pharmacodynamic interactions were observed with aspirin, clopidogrel, or prasugrel *[see Warnings and Precautions (5.2)]*. A 50% to 60% increase in anti-FXa activity was observed when apixaban was coadministered with enoxaparin or naproxen.

Specific Populations

Renal impairment: Anti-FXa activity adjusted for exposure to apixaban was similar across renal function categories.

Hepatic impairment: Changes in anti-FXa activity were similar in patients with mild-to-moderate hepatic impairment and healthy subjects. However, in patients with moderate hepatic impairment, there is no clear understanding of the impact of this degree of hepatic function impairment on the coagulation cascade and its relationship to efficacy and bleeding. Patients with severe hepatic impairment were not studied.

Cardiac Electrophysiology

Apixaban has no effect on the QTc interval in humans at doses up to 50 mg.

12.3 Pharmacokinetics

Apixaban demonstrates linear pharmacokinetics with dose-proportional increases in exposure for oral doses up to 10 mg.

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg of ELIQUIS. Food does not affect the bioavailability of apixaban. Maximum concentrations (C_{max}) of apixaban appear 3 to 4 hours after oral administration of ELIQUIS. At doses ≥25 mg, apixaban displays dissolution-limited absorption with decreased bioavailability. Following administration of a crushed 5 mg ELIQUIS tablet that was suspended in 60 mL D5W and delivered through a nasogastric tube (NGT), exposure was similar to that seen in other clinical trials involving healthy volunteers receiving a single oral 5 mg tablet dose.

Distribution

Plasma protein binding in humans is approximately 87%. The volume of distribution (Vss) is approximately 21 liters.

Metabolism

Approximately 25% of an orally administered apixaban dose is recovered in urine and feces as metabolites. Apixaban is metabolized mainly via CYP3A4 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation.

Unchanged apixaban is the major drug-related component in human plasma; there are no active circulating metabolites.

Elimination

Apixaban is eliminated in both urine and feces. Renal excretion accounts for about 27% of total clearance. Biliary and direct intestinal excretion contributes to elimination of apixaban in the feces.

Apixaban has a total clearance of approximately 3.3 L/hour and an apparent half-life of approximately 12 hours following oral administration.

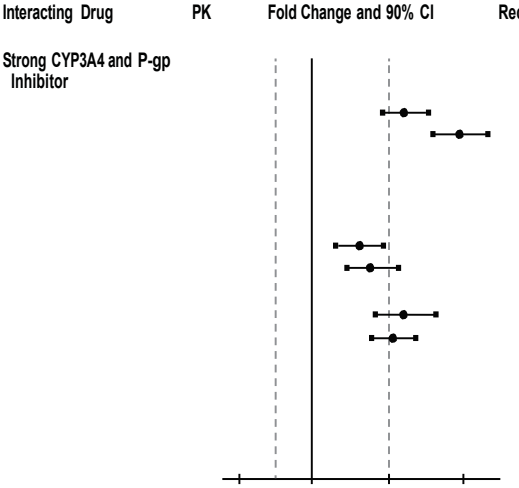
Apixaban is a substrate of transport proteins: P-gp and breast cancer resistance protein.

Drug Interaction Studies

In vitro apixaban studies at concentrations significantly greater than therapeutic exposures, no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A4/5, or CYP2C19, nor induction effect on the activity of CYP1A2, CYP2B6, or CYP3A4/5 were observed. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolized by these enzymes. Apixaban is not a significant inhibitor of P-gp.

The effects of coadministered drugs on the pharmacokinetics of apixaban and associated dose recommendations are summarized in Figure 2 *[see also Warnings and Precautions (5.2) and Drug Interactions (7)]*.

Figure 2: Effect of Coadministered Drugs on the Pharmacokinetics of Apixaban



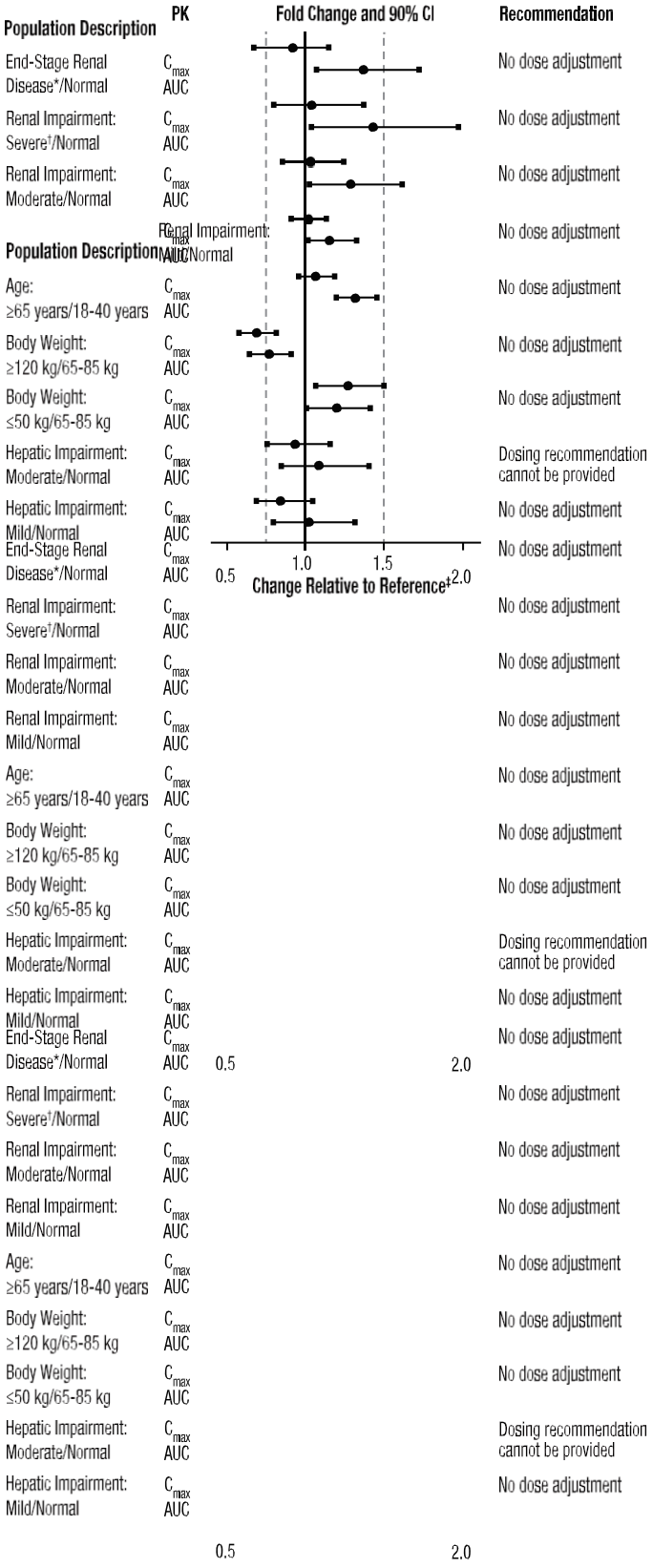
In dedicated studies conducted in healthy subjects, famotidine, atenolol, prasugrel, and enoxaparin did not meaningfully alter the pharmacokinetics of apixaban.

In studies conducted in healthy subjects, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, atenolol, prasugrel, or acetylsalicylic acid.

Specific Populations

The effects of level of renal impairment, age, body weight, and level of hepatic impairment on the pharmacokinetics of apixaban are summarized in Figure 3.

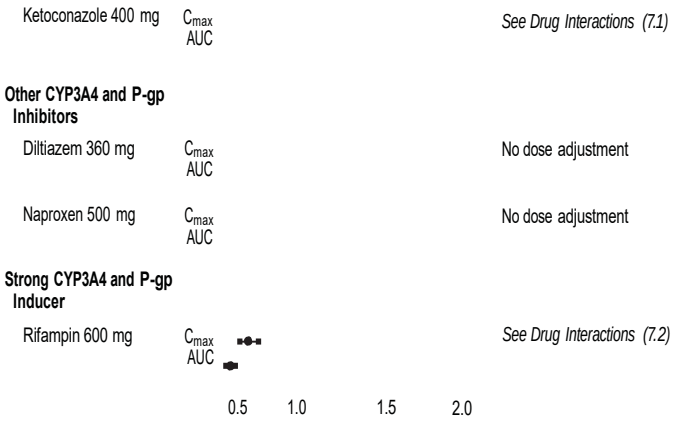
Figure 3: Effect of Specific Populations on the Pharmacokinetics of Apixaban



* ESRD subjects maintained with chronic and stable hemodialysis; reported PK findings are following single dose of apixaban post hemodialysis.

† Creatinine clearance 15 to 29 mL/min.

‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.



* Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations. Dosing recommendations were also informed by clinical considerations *[see Warnings and Precautions (5.2) and Drug Interactions (7)].*

A study in healthy subjects comparing the pharmacokinetics in males and females showed no meaningful difference.

The results across pharmacokinetic studies in normal subjects showed no differences in apixaban pharmacokinetics among White/Caucasian, Asian, and Black/African American subjects. No dose adjustment is required based on race/ethnicity.

In subjects with ESRD, a 4-hour hemodialysis session with a dialysate flow rate of 500 mL/min and a blood flow rate in the range of 350 to 500 mL/min started 2 hours after administration of a single 5 mg dose of apixaban, the AUC of apixaban was 17% greater compared to those with normal renal function. The dialysis clearance of apixaban is approximately 18 mL/min resulting in a 14% decrease in exposure due to hemodialysis compared to off-dialysis period.

Protein binding was similar (92%-94%) between healthy controls and the on-dialysis and off-dialysis periods.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Apixaban was not carcinogenic when administered to mice and rats for up to 2 years. The systemic exposures (AUCs) of unbound apixaban in male and female mice at the highest doses tested (1500 and 3000 mg/kg/day) were 9 and 20 times, respectively, the human exposure of unbound drug at the MRHD of 10 mg/day. Systemic exposures of unbound apixaban in male and female rats at the highest dose tested (600 mg/kg/day) were 2 and 4 times, respectively, the human exposure.

Mutagenesis: Apixaban was neither mutagenic in the bacterial reverse mutation (Ames) assay, nor clastogenic in Chinese hamster ovary cells *in vitro*, in a 1-month *in vivo/in vitro* cytogenetics study in rat peripheral blood lymphocytes, or in a rat micronucleus study *in vivo*.

Impairment of Fertility: Apixaban had no effect on fertility in male or female rats when given at doses up to 600 mg/kg/day, a dose resulting in exposure levels that are 3 and 4 times, respectively, the human exposure.

Apixaban administered to female rats at doses up to 1000 mg/kg/day from implantation through the end of lactation produced no adverse findings in male offspring

(F_1 generation) at doses up to 1000 mg/kg/day, a dose resulting in exposure that is 5 times the human exposure. Adverse effects in the F_1-generation female offspring were limited to decreased mating and fertility indices at 1000 mg/kg/day.

14 CLINICAL STUDIES

14.1 Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation

ARISTOTLE

Evidence for the efficacy and safety of ELIQUIS was derived from ARISTOTLE, a multinational, double-blind study in patients with nonvalvular AF comparing the effects of ELIQUIS and warfarin on the risk of stroke and non-central nervous system (CNS) systemic embolism. In ARISTOTLE, patients were randomized to ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in subjects with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL) or to warfarin (targeted to an INR range of 2.0–3.0). Patients had to have one or more of the following additional risk factors for stroke:

- prior stroke or transient ischemic attack (TIA)
- prior systemic embolism
- age ≥75 years
- arterial hypertension requiring treatment
- diabetes mellitus
- heart failure ≥New York Heart Association Class 2
- left ventricular ejection fraction ≤40%

The primary objective of ARISTOTLE was to determine whether ELIQUIS 5 mg twice daily (or 2.5 mg twice daily) was effective (noninferior to warfarin) in reducing the risk of stroke (ischemic or hemorrhagic) and systemic embolism. Superiority of ELIQUIS to warfarin was also examined for the primary endpoint (rate of stroke and systemic embolism), major bleeding, and death from any cause.

A total of 18,201 patients were randomized and followed on study treatment for a median of 89 weeks. Forty-three percent of patients were vitamin K antagonist (VKA) "naive," defined as having received ≤30 consecutive days of treatment with warfarin or another VKA before entering the study. The mean age was 69 years and the mean $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk) was 2.1. The population was 65% male, 83% Caucasian, 14% Asian, and 1% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 19% of patients. Concomitant diseases of patients in this study included hypertension 88%, diabetes 25%, congestive heart failure (or left ventricular ejection fraction ≤40%) 35%, and prior myocardial infarction 14%. Patients treated with warfarin in ARISTOTLE had a mean percentage of time in therapeutic range (INR 2.0–3.0) of 62%.

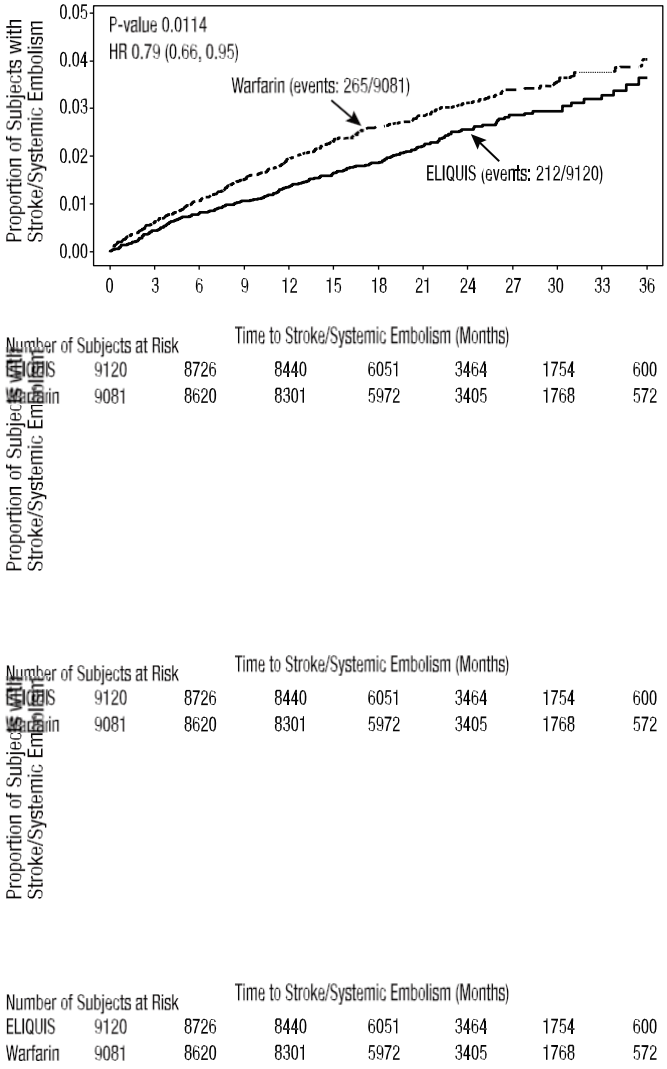
ELIQUIS was superior to warfarin for the primary endpoint of reducing the risk of stroke and systemic embolism (Table 9 and Figure 4). Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs.

ELIQUIS also showed significantly fewer major bleeds than warfarin *[see Adverse Reactions (6.1)]*.

Table 9: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE (Intent-to-Treat Analysis)

	ELIQUIS N=9120 n (%/year)	Warfarin N=9081 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	212 (1.27)	265 (1.60)	0.79 (0.66, 0.95)	0.01
Stroke	199 (1.19)	250 (1.51)	0.79 (0.65, 0.95)	
Ischemic without hemorrhage	140 (0.83)	136 (0.82)	1.02 (0.81, 1.29)	
Ischemic with hemorrhagic conversion	12 (0.07)	20 (0.12)	0.60 (0.29, 1.23)	
Hemorrhagic	40 (0.24)	78 (0.47)	0.51 (0.35, 0.75)	

Figure 4: Kaplan-Meier Estimate of Time to First Stroke or Systemic Embolism in ARISTOTLE (Intent-to-Treat Population)



All-cause death was assessed using a sequential testing strategy that allowed testing for superiority if effects on earlier endpoints (stroke plus systemic embolus and major bleeding) were demonstrated. ELIQUIS treatment resulted in a significantly lower rate of all-cause death (p = 0.046) than did treatment with warfarin, primarily because of a reduction in cardiovascular death, particularly stroke deaths. Non-vascular death rates were similar in the treatment arms.

In ARISTOTLE, the results for the primary efficacy endpoint were generally consistent across most major subgroups including weight, $CHADS_2$ score (a scale from 0 to 6 used to predict risk of stroke in patients with AF, with higher scores predicting greater risk), prior warfarin use, level of renal impairment, geographic region, ELIQUIS dose, type of AF, and aspirin use at randomization (Figure 5).

Unknown	14 (0.08)	21 (0.13)	0.65 (0.33, 1.29)
Systemic embolism	15 (0.09)	17 (0.10)	0.87 (0.44, 1.75)

The primary endpoint was based on the time to first event (one per subject). Component counts are for subjects with any event, not necessarily the first.

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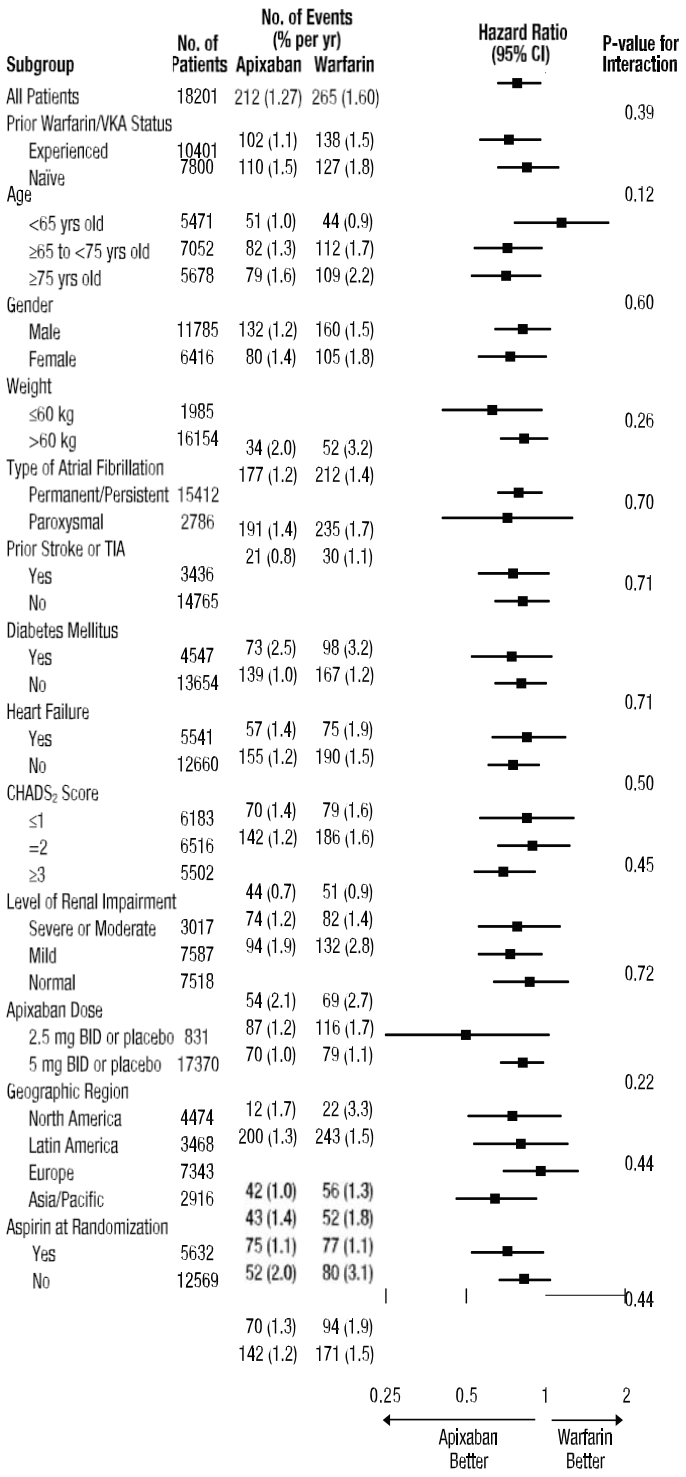
Figure 5: Stroke and Systemic Embolism Hazard Ratios by Baseline Characteristics – ARISTOTLE Study



At the end of the ARISTOTLE study, warfarin patients who completed the study were generally maintained on a VKA with no interruption of anticoagulation. ELIQUIS patients who completed the study were generally switched to a VKA with a 2-day period of coadministration of ELIQUIS and VKA, so that some patients may not have been adequately anticoagulated after stopping ELIQUIS until attaining a stable and therapeutic INR. During the 30 days following the end of the study, there were 21 stroke or systemic embolism events in the 6791 patients (0.3%) in the ELIQUIS arm compared to 5 in the 6569 patients (0.1%) in the warfarin arm *[see Dosage and Administration (2.5)]*.

AVERROES

In AVERROES, patients with nonvalvular atrial fibrillation thought not to be candidates for warfarin therapy were randomized to treatment with ELIQUIS 5 mg orally twice daily (or 2.5 mg twice daily in selected patients) or aspirin 81 to 324 mg once daily. The primary objective of the study was to determine if ELIQUIS was superior to aspirin for preventing the composite outcome of stroke or systemic embolism. AVERROES was stopped early on the basis of a prespecified interim analysis showing a significant reduction in stroke and systemic embolism for ELIQUIS compared to aspirin that was associated with a modest increase in major bleeding (Table 10) *[see Adverse Reactions (6.1)]*.

Table 10: Key Efficacy Outcomes in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS N=2807 n (%/year)	Aspirin N=2791 n (%/year)	Hazard Ratio (95% CI)	P-value
Stroke or systemic embolism	51 (1.62)	113 (3.63)	0.45 (0.32, 0.62)	<0.0001
Stroke				
Ischemic or undetermined	43 (1.37)	97 (3.11)	0.44 (0.31, 0.63)	-
Hemorrhagic	6 (0.19)	9 (0.28)	0.67 (0.24, 1.88)	-
Systemic embolism	2 (0.06)	13 (0.41)	0.15 (0.03, 0.68)	-
MI	24 (0.76)	28 (0.89)	0.86 (0.50, 1.48)	-
All-cause death	111 (3.51)	140 (4.42)	0.79 (0.62, 1.02)	0.068
Vascular death	84 (2.65)	96 (3.03)	0.87 (0.65, 1.17)	-

14.2 Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The clinical evidence for the effectiveness of ELIQUIS is derived from the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical trials in adult patients undergoing elective hip (ADVANCE-3) or knee (ADVANCE-2 and ADVANCE-1) replacement surgery. A total of 11,659 patients were randomized in 3 double-blind, multi-national studies. Included in this total were 1866 patients age 75 or older, 1161 patients with low body weight (≤60 kg), 2528 patients with Body Mass Index ≥33 kg/m^2, and 625 patients with severe or moderate renal impairment.

In the ADVANCE-3 study, 5407 patients undergoing elective hip replacement surgery were randomized to receive either ELIQUIS 2.5 mg orally twice daily or enoxaparin 40 mg subcutaneously once daily. The first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Treatment duration was 32 to 38 days.

In patients undergoing elective knee replacement surgery, ELIQUIS 2.5 mg orally twice daily was compared to enoxaparin 40 mg subcutaneously once daily (ADVANCE-2, N=3057) or enoxaparin 30 mg subcutaneously every 12 hours (ADVANCE-1, N=3195). In the ADVANCE-2 study, the first dose of ELIQUIS was given 12 to 24 hours post surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. In the ADVANCE-1 study, both ELIQUIS and enoxaparin were initiated 12 to 24 hours post surgery. Treatment duration in both ADVANCE-2 and ADVANCE-1 was 10 to 14 days.

In all 3 studies, the primary endpoint was a composite of adjudicated asymptomatic and symptomatic DVT, nonfatal PE, and all-cause death at the end of the double-blind intended treatment period. In ADVANCE-3 and ADVANCE-2, the primary endpoint was tested for noninferiority, then superiority, of ELIQUIS to enoxaparin. In ADVANCE-1, the primary endpoint was tested for noninferiority of ELIQUIS to enoxaparin.

The efficacy data are provided in Tables 11 and 12.

Table 11: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Hip Replacement Surgery*

	ADVANCE-3		
Events During 35-Day Treatment Period	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1949**	**N=1917**	
Total VTE†/All-cause death	27 (1.39%) (0.95, 2.02)	74 (3.86%) (3.08, 4.83)	0.36 (0.22, 0.54) p<0.0001
Number of Patients	**N=2708**	**N=2699**	
All-cause death	3 (0.11%) (0.02, 0.35)	1 (0.04%) (0.00, 0.24)	
PE	3 (0.11%) (0.02, 0.35)	5 (0.19%) (0.07, 0.45)	
Symptomatic DVT	1 (0.04%) (0.00, 0.24)	5 (0.19%) (0.07, 0.45)	
Number of Patients	**N=2196**	**N=2190**	
Proximal DVT‡	7 (0.32%) (0.14, 0.68)	20 (0.91%) (0.59, 1.42)	
Number of Patients	**N=1951**	**N=1908**	
Distal DVT‡	20 (1.03%) (0.66, 1.59)	57 (2.99%) (2.31, 3.86)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
† Total VTE includes symptomatic and asymptomatic DVT and PE.
‡ Includes symptomatic and asymptomatic DVT.

Table 12: Summary of Key Efficacy Analysis Results During the Intended Treatment Period for Patients Undergoing Elective Knee Replacement Surgery*

	ADVANCE-1			ADVANCE-2		
Events during 12-day treatment period	ELIQUIS 2.5 mg po bid	Enoxaparin 30 mg sc q12h	Relative Risk (95% CI) P-value	ELIQUIS 2.5 mg po bid	Enoxaparin 40 mg sc qd	Relative Risk (95% CI) P-value
Number of Patients	**N=1157**	**N=1130**		**N=976**	**N=997**	
Total VTE†/ All-cause death	104 (8.99%) (7.47, 10.79)	100 (8.85%) (7.33, 10.66)	1.02 (0.78, 1.32) NS	147 (15.06%) (12.95, 17.46)	243 (24.37%) (21.81, 27.14)	0.62 (0.51, 0.74) p<0.0001
Number of Patients	**N=1599**	**N=1596**		**N=1528**	**N=1529**	
All-cause death	3 (0.19%) (0.04, 0.59)	3 (0.19%) (0.04, 0.59)		2 (0.13%) (0.01, 0.52)	0 (0%) (0.00, 0.31)	
PE	16 (1.0%) (0.61, 1.64)	7 (0.44%) (0.20, 0.93)		4 (0.26%) (0.08, 0.70)	0 (0%) (0.00, 0.31)	
Symptomatic DVT	3 (0.19%) (0.04, 0.59)	7 (0.44%) (0.20, 0.93)		3 (0.20%) (0.04, 0.61)	7 (0.46%) (0.20, 0.97)	
Number of Patients	**N=1254**	**N=1207**		**N=1192**	**N=1199**	
Proximal DVT‡	9 (0.72%) (0.36, 1.39)	11 (0.91%) (0.49, 1.65)		9 (0.76%) (0.38, 1.46)	26 (2.17%) (1.47, 3.18)	
Number of Patients	**N=1146**	**N=1133**		**N=978**	**N=1000**	
Distal DVT‡	83 (7.24%) (5.88, 8.91)	91 (8.03%) (6.58, 9.78)		142 (14.52%) (12.45, 16.88)	239 (23.9%) (21.36, 26.65)	

* Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints.
† Total VTE includes symptomatic and asymptomatic DVT and PE.
‡ Includes symptomatic and asymptomatic DVT.

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14.3 Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

Efficacy and safety of ELIQUIS for the treatment of DVT and PE, and for the reduction in the risk of recurrent DVT and PE following 6 to 12 months of anticoagulant treatment was derived from the AMPLIFY and AMPLIFY-EXT studies. Both studies were randomized, parallel-group, double-blind trials in patients with symptomatic proximal DVT and/or symptomatic PE. All key safety and efficacy endpoints were adjudicated in a blinded manner by an independent committee.

AMPLIFY

The primary objective of AMPLIFY was to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent VTE (venous thromboembolism) or VTE-related death. Patients with an objectively confirmed symptomatic DVT and/or PE were randomized to treatment with ELIQUIS 10 mg twice daily orally for 7 days followed by ELIQUIS 5 mg twice daily orally for 6 months, or enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2) followed by warfarin (target INR range 2.0-3.0) orally for 6 months. Patients who required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, and patients with creatinine clearance <25 mL/min, significant liver disease, an existing heart valve or atrial fibrillation, or active bleeding were excluded from the AMPLIFY study. Patients were allowed to enter the study with or without prior parenteral anticoagulation (up to 48 hours).

A total of 5244 patients were evaluable for efficacy and were followed for a mean of 154 days in the ELIQUIS group and 152 days in the enoxaparin/warfarin group. The mean age was 57 years. The AMPLIFY study population was 59% male, 83% Caucasian, 8% Asian, and 4% Black. For patients randomized to warfarin, the mean percentage of time in therapeutic range (INR 2.0-3.0) was 60.9%.

Approximately 90% of patients enrolled in AMPLIFY had an unprovoked DVT or PE at baseline. The remaining 10% of patients with a provoked DVT or PE were required to have an additional ongoing risk factor in order to be randomized, which included previous episode of DVT or PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

ELIQUIS was shown to be noninferior to enoxaparin/warfarin in the AMPLIFY study for the primary endpoint of recurrent symptomatic VTE (nonfatal DVT or nonfatal PE) or VTE-related death over 6 months of therapy (Table 13).

Table 13: Efficacy Results in the AMPLIFY Study

	ELIQUIS N=2609 n	Enoxaparin/Warfarin N=2635 n	Relative Risk (95% CI)
VTE or VTE-related death*	59 (2.3%)	71 (2.7%)	0.84 (0.60, 1.18)
DVT†	22 (0.8%)	35 (1.3%)	
PE†	27 (1.0%)	25 (0.9%)	
VTE-related death†	12 (0.4%)	16 (0.6%)	
VTE or all-cause death	84 (3.2%)	104 (4.0%)	0.82 (0.61, 1.08)
VTE or CV-related death	61 (2.3%)	77 (2.9%)	0.80 (0.57, 1.11)

The efficacy profile of ELIQUIS was generally consistent across subgroups of interest for this indication (e.g., age, gender, race, body weight, renal impairment).

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* Noninferior compared to enoxaparin/warfarin (P-value <0.0001).

† Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

In the AMPLIFY study, patients were stratified according to their index event of PE (with or without DVT) or DVT (without PE). Efficacy in the initial treatment of VTE was consistent between the two subgroups.

AMPLIFY-EXT

Patients who had been treated for DVT and/or PE for 6 to 12 months with anticoagulant therapy without having a recurrent event were randomized to treatment with ELIQUIS 2.5 mg orally twice daily, ELIQUIS 5 mg orally twice daily, or placebo for 12 months. Approximately one-third of patients participated in the AMPLIFY study prior to enrollment in the AMPLIFY-EXT study.

A total of 2482 patients were randomized to study treatment and were followed for a mean of approximately 330 days in the ELIQUIS group and 312 days in the placebo group. The mean age in the AMPLIFY-EXT study was 57 years. The study population was 57% male, 85% Caucasian, 5% Asian, and 3% Black.

The AMPLIFY-EXT study enrolled patients with either an unprovoked DVT or PE at baseline (approximately 92%) or patients with a provoked baseline event and one additional risk factor for recurrence (approximately 8%). However, patients who had experienced multiple episodes of unprovoked DVT or PE were excluded from the AMPLIFY-EXT study. In the AMPLIFY-EXT study, both doses of ELIQUIS were superior to placebo in the primary endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE), or all-cause death (Table 14).

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Table 14: Efficacy Results in the AMPLIFY-EXT Study

				Relative Risk (95% CI)	
	ELIQUIS 2.5 mg N=840	ELIQUIS 5 mg N=813	Placebo N=829	ELIQUIS 2.5 mg vs Placebo	ELIQUIS 5 mg vs Placebo
	n (%)				
Recurrent VTE or all-cause death	32 (3.8)	34 (4.2)	96 (11.6)	0.33 (0.22, 0.48) p<0.0001	0.36 (0.25, 0.53) p<0.0001
DVT*	19 (2.3)	28 (3.4)	72 (8.7)		
PE*	23 (2.7)	25 (3.1)	37 (4.5)		
All-cause death	22 (2.6)	25 (3.1)	33 (4.0)		

* Patients with more than one event are counted in multiple rows.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ELIQUIS (apixaban) tablets are available as listed in the table below.

Tablet Strength	Tablet Color/Shape	Tablet Markings	Package Size	NDC Code
2.5 mg	Yellow, round, biconvex	Debossed with "893" on one side and "2½" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0893-21 0003-0893-41 0003-0893-31
5 mg	Pink, oval, biconvex	Debossed with "894" on one side and "5" on the other side	Bottles of 60 Bottles of 180 Hospital Unit-Dose Blister Package of 100	0003-0894-21 0003-0894-41 0003-0894-31

Storage and Handling

Store at 20°C to 25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F-86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- They should not discontinue ELIQUIS without talking to their physician first.
- They should be informed that it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- They should tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas, such as numbness or weakness of the legs, or bowel or bladder dysfunction *[see Warnings and Precautions (5.3)]*. If any of these symptoms occur, the patient should contact his or her physician immediately.
- They should tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations (8.1, 8.3)].*
- If a dose is missed, the dose should be taken as soon as possible on the same day and twice-daily administration should be resumed. The dose should not be doubled to make up for a missed dose.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543 USA

and

Pfizer Inc
New York, New York 10017 USA

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Appendix 7: Apixaban Patient Information

℞ ONLY MEDICATION GUIDE

ELIQUIS® (ELL eh kwiss) **(apixaban) tablets**

What is the most important information I should know about ELIQUIS?

- **For people taking ELIQUIS for atrial fibrillation:**

  People with atrial fibrillation (a type of irregular heartbeat) are at an increased risk of forming a blood clot in the heart, which can travel to the brain, causing a stroke, or to other parts of the body. ELIQUIS lowers your chance of having a stroke by helping to prevent clots from forming. If you stop taking ELIQUIS, you may have increased risk of forming a clot in your blood.

  Do not stop taking ELIQUIS without talking to the doctor who prescribes it for you. Stopping ELIQUIS increases your risk of having a stroke.

  ELIQUIS may need to be stopped, if possible, prior to surgery or a medical or dental procedure. Ask the doctor who prescribed ELIQUIS for you when you should stop taking it. Your doctor will tell you when you may start taking ELIQUIS again after your surgery or procedure. If you have to stop taking ELIQUIS, your doctor may prescribe another medicine to help prevent a blood clot from forming.

- **ELIQUIS can cause bleeding** which can be serious and rarely may lead to death. This is because ELIQUIS is a blood thinner medicine that reduces blood clotting.

  You may have a higher risk of bleeding if you take ELIQUIS and take other medicines that increase your risk of bleeding, including:

  - aspirin or aspirin-containing products
  - long-term (chronic) use of nonsteroidal anti-inflammatory drugs (NSAIDs)
  - warfarin sodium (COUMADIN®, JANTOVEN®)
  - any medicine that contains heparin
  - selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs)
  - other medicines to help prevent or treat blood clots

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Tell your doctor if you take any of these medicines. Ask your doctor or pharmacist if you are not sure if your medicine is one listed above.

While taking ELIQUIS:

- you may bruise more easily
- it may take longer than usual for any bleeding to stop

Call your doctor or get medical help right away if you have any of these signs or symptoms of bleeding when taking ELIQUIS:

- unexpected bleeding, or bleeding that lasts a long time, such as:
  - unusual bleeding from the gums
  - nosebleeds that happen often
  - menstrual bleeding or vaginal bleeding that is heavier than normal
- bleeding that is severe or you cannot control
- red, pink, or brown urine
- red or black stools (looks like tar)
- cough up blood or blood clots
- vomit blood or your vomit looks like coffee grounds
- unexpected pain, swelling, or joint pain
- headaches, feeling dizzy or weak

- **ELIQUIS is not for patients with artificial heart valves.**
- **Spinal or epidural blood clots (hematoma).** People who take a blood thinner medicine (anticoagulant) like ELIQUIS, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:
  - a thin tube called an epidural catheter is placed in your back to give you certain medicine

- you take NSAIDs or a medicine to prevent blood from clotting
- you have a history of difficult or repeated epidural or spinal punctures
- you have a history of problems with your spine or have had surgery on your spine

If you take ELIQUIS and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots or bleeding. Tell your doctor right away if you have tingling, numbness, or muscle weakness, especially in your legs and feet.

What is ELIQUIS?

ELIQUIS is a prescription medicine used to:

- reduce the risk of stroke and blood clots in people who have atrial fibrillation.
- reduce the risk of forming a blood clot in the legs and lungs of people who have just had hip or knee replacement surgery.
- treat blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism), and reduce the risk of them occurring again.

It is not known if ELIQUIS is safe and effective in children.

Who should not take

ELIQUIS? Do not take

ELIQUIS if you:

- currently have certain types of abnormal bleeding.
- have had a serious allergic reaction to

ELIQUIS. Ask your doctor if you are not sure.

What should I tell my doctor before taking
ELIQUIS?

Before you take ELIQUIS, tell your doctor if you:

- have kidney or liver problems
- have any other medical condition
- have ever had bleeding problems
- are pregnant or plan to become pregnant.

It is not known if ELIQUIS will harm your unborn baby.

- are breastfeeding or plan to breastfeed. It is not known if ELIQUIS passes into your breast milk. You and your doctor should decide if you will take ELIQUIS or breastfeed. You should not do both.

Tell all of your doctors and dentists that you are taking ELIQUIS. They should talk to the doctor who prescribed ELIQUIS for you, before you have **any** surgery, medical or dental procedure.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Some of your other medicines may affect the way ELIQUIS works. Certain medicines may increase your risk of bleeding or stroke when taken with ELIQUIS. See "**What is the most important information I should know about ELIQUIS?**"

Know the medicines you take. Keep a list of them to show your doctor and pharmacist when you get a new medicine.

How should I take ELIQUIS?

- **Take ELIQUIS exactly as prescribed by your doctor.**
- Take ELIQUIS twice every day with or without food.
- Do not change your dose or stop taking ELIQUIS unless your doctor tells you to.
- If you miss a dose of ELIQUIS, take it as soon as you remember. Do not take more than one dose of ELIQUIS at the same time to make up for a missed dose.
- Your doctor will decide how long you should take ELIQUIS. **Do not stop taking it without first talking with your doctor. If you are taking ELIQUIS for atrial fibrillation, stopping ELIQUIS may increase your risk of having a stroke**.

- **Do not run out of ELIQUIS. Refill your prescription before you run out.** When leaving the hospital following hip or knee replacement, be sure that you will have ELIQUIS available to avoid missing any doses.
- If you take too much ELIQUIS, call your doctor or go to the nearest hospital emergency room right away.

- Call your doctor or healthcare provider right away if you fall or injure yourself, especially if you hit your head. Your doctor or healthcare provider may need to check you.

What are the possible side effects of ELIQUIS?

- See "**What is the most important information I should know about ELIQUIS?**"
- ELIQUIS can cause a skin rash or severe allergic reaction. Call your doctor or get medical help right away if you have any of the following symptoms:
  - chest pain or tightness
  - swelling of your face or tongue
  - trouble breathing or wheezing
  - feeling dizzy or faint

Tell your doctor if you have any side effect that bothers you or that does not go away.

These are not all of the possible side effects of ELIQUIS. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ELIQUIS?

What are the ingredients in ELIQUIS?

Active ingredient: apixaban.

Inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, triacetin, and yellow iron oxide (2.5 mg tablets) or red iron oxide (5 mg tablets).

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543
USA

Marketed by:
Bristol-Myers Squibb Company
Princeton, New Jersey 08543
USA and
Pfizer Inc
New York, New York 10017
USA

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Store ELIQUIS at room temperature between 68°F to 77°F (20°C to 25°C).

Keep ELIQUIS and all medicines out of the reach of children.

General Information about ELIQUIS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ELIQUIS for a condition for which it was not prescribed. Do not give ELIQUIS to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about ELIQUIS that is written for health professionals.

For more information call 1-855-354-7847 (1-855-ELIQUIS) or go to www.ELIQUIS.com.

Revised August 2014
432US14BR00805-06-01