Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Apixaban

Proprietary Product Name: Eliquis

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

September 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission:	New Chemical Entity
Decision:	Approved
Date of Decision:	14 July 2011
Active ingredient(s):	Apixaban
Product Name(s):	Eliquis
Sponsor's Name and Address:	Bristol-Myers Squibb Australia Pty Ltd 556 Princes Highway Noble Park VIC 3174
Dose form(s):	Film coated tablet
Strength(s):	2.5 mg
Container(s):	Blister pack
Pack size(s):	10, 20, 30, 60 or 100 tablets
Approved Therapeutic use:	For the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.
Route(s) of administration:	Oral
Dosage:	2.5 mg twice daily for 10-14 days (knee replacement surgery) or 32-38 days (hip replacement surgery).
ARTG Number:	172244

Product Background

The Western Australian Data Linkage System has been used to estimate a prevalence of venous thromboembolism (VTE) in all hospital admissions of around 2 to 3 per 1000 with the highest prevalence found in cancer, musculoskeletal, cardiovascular and respiratory patient groups.[1] Patients undergoing total hip replacement (THR) are in the highest risk category for VTE, on the basis of the procedure itself, and in the absence of thromboprophylaxis, the risk of VTE is high following THR.[2] There is general consensus

[1] National Institute of Clinical Studies. The incidence and risk factors for venous thromboembolism in hospitals in Western Australia 1999-2001. Prepared by the School of Population Health, University of Western Australia. NICS, Melbourne [internet]. 2005. Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/nics/material_resources/The%20incidence%20of%20venous%20thromboembolism%20in%20Western%20Australian%20hospitals.pdf.

[2] National Health and Medical Research Council. Clinical practice guideline for the prevention of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in patients admitted to Australian hospitals. Melbourne: National Health and Medical Research Council [internet]. 2009. Available from: http://www.nhmrc.gov.au/_files_nhmrc/file/nics/programs/vtp/guideline_prevention_venous_thromboembolism.pdf.

for the use of pharmacological thromboprophylaxis in the absence of contraindications, for patients admitted for THR (Clinical Practice Guideline, NHMRC).[2] Similarly, patients undergoing total knee replacement (TKR) are in one of the highest risk categories for VTE and should also receive thromboprophylaxis after surgery.[2] In 2009 there were 33,943 hip replacements reported in Australia to the National Joint Replacement Registry of which 71.5% were for primary total hip replacements.[3] There were 40,675 knee replacements reported to the registry for the same year.[3] The National Joint Replacement Registry receives information on nearly all hip and knee replacements undertaken in Australia. Therefore the Australian population exposure to pharmacological thromboprophylaxis is likely to be fairly large.

Apixaban is a new chemical entity being developed for the prevention and treatment of VTE and for the prevention of stroke and systemic embolism in patients with atrial fibrillation (AF). Apixaban is an orally active, selective, direct inhibitor of the coagulation factor Xa (FXa) that reversibly and directly binds to the active site of FXa. It exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. A similar orally acting drug (FXa inhibitor), rivaroxaban (Xarelto), was registered in 2008 for the prevention of VTE in adult patients who have undergone major orthopaedic surgery of the lower limbs: elective TKR or elective THR. A subcutaneously administered FXa inhibitor, fondaparinux (Arixtra), was registered in 2005 for the prevention of VTE in patients undergoing major orthopaedic surgery of the lower limbs and patients undergoing abdominal surgery who are at risk of thromboembolic complications. Fondaparinux is also registered for the treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE).

This AusPAR describes the evaluation of an application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register Eliquis containing apixaban for the following indication:

Eliquis is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery.

The proposed dosage regimen outlined in the proposed product information (PI) is:

- 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 32 to 38 days.
- In patients undergoing knee replacement surgery, the recommended duration of treatment is 10 to 14 days.

Regulatory Status

A similar application was submitted in the European Union (EU) and approved on 18 May 2011 for the same indication (which is identical to the proposed Australian indication):

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

[3] Australian Orthopaedic Association National Joint Replacement Registry. Annual Report. Adelaide: AOA [internet]. 2010. Available from: http://www.dmac.adelaide.edu.au/aoanjrr/documents/aoanjrrreport_2010.pdf

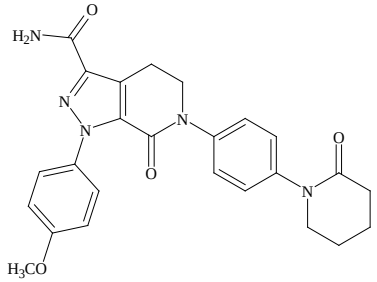
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Apixaban is prepared in a purely synthetic multiple step process. It is achiral and BCS Class III (high solubility low permeability).[4] Apixaban is manufactured by Swords Laboratories Ltd in County Dublin, Ireland.



apixaban

$C_{25}H_{25}N_5O_4$ MW = 459.5 CAS # = [503612-47-3]

The solubility is independent of pH and low: 0.04 mg/ml (0.004%, practically insoluble)

The specifications include tests and limits for four nominated related substances. The limit for one of these was above the International Council on Harmonisation (ICH) qualification limit but toxicological data to support the limit were assessed (see Section III).[5] The other known impurities are controlled to the ICH qualification threshold and unknown impurities to the ICH identification threshold of NMT 0.10%.

The residual solvents are limited to ICH levels. The particle size distribution is controlled. No polymorphs are known.

Drug Product

Formulation and manufacture

The tablets are manufactured by Bristol-Myers Squibb Manufacturing Company in Humacao, Puerto Rico. The process (which is a simple dry granulation process) was extensively validated using the quality by design approach and included appropriate in-process controls.

[4] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

[5] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an individual impurity or a given impurity profile at the level(s) specified.

The cores of the tablets are made by dry granulation, milling, blending and compression. The particle size of the drug substance affects the dissolution performance and a low limit has been set.

Specifications

Assay limits at expiry comply with Therapeutic Goods Order 56/78. The limits for degradants comply with ICH guidance.

The sponsor proposed to use a disintegration test rather than a dissolution test but provided extensive data to justify this procedure.

Stability

The only change to the product on storage was an increase in the water content but this had no affect on chemical or physical stability and the stability data provided supported a shelf life of 3 years when stored below 30ºC in PVC\PVDC/Al blister packs.

Biopharmaceutics

The Phase III clinical efficacy studies were performed using 2.5 mg and 5 mg tablets. These were direct scales of each other and given that the pharmacokinetics are linear up to 10 mg, 2 x 2.5 mg tablets can be considered bioequivalent to the 5 mg tablet.

The 2.5 mg tablet proposed for marketing differs from that used in the Phase III clinical efficacy studies only in that the film coat was slightly different. This change did not affect the dissolution rate and it was accepted that these formulations are bioequivalent.

To support registration, four bioavailability studies were provided.

Results

Study CV185024 was performed to determine if there was any *in vivo*, *in vitro* correlation (IVIVC). The area under the plasma concentration time curve (AUC) was not significantly affected by the amount dissolved in 30 minutes using a potential dissolution test method, but the maximum plasma concentration (C_{max}) was affected. This fact was used to set appropriate limits for the particle size distribution of apixaban and dissolution rate of the finished product. This study also indicated that Phase II and Phase III tablets with similar dissolution rates were bioequivalent.

In study CV185045 the absolute bioavailability was estimated to be 50% using a 10 mg tablet and a 5 mg intravenous (IV) injection. Given that the pharmacokinetics are linear up to 10 mg, this result is relevant to the proposed 2.5 mg tablet.

In study CV185008, the effect of food was tested on a 5 mg tablet. No effect was observed. Given that the pharmacokinetics are linear up to 10 mg, this result is relevant to the proposed 2.5 mg tablet.

Study CV185019 was also provided which showed the bioequivalence of 2 x Phase II 10 mg tablets to two potential Phase III 20 mg tablets manufactured by wet and dry granulation methods. The dry granulation formulation was chosen for further development into the 2.5 mg and 5 mg Phase III tablets.

Advisory Committee Considerations

This application was presented to the 137th meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC had no objections to approval of the submission provided all outstanding issues were addressed to the satisfaction of the TGA, which was the case.

The Committee considered the use of a disintegration test as a surrogate for a dissolution test unacceptable especially as the correlation between the two parameters was very poor. The Committee therefore agreed that the sponsor should either include a suitable dissolution test in the finished product specifications or provide appropriate justification for the absence of such a test. As noted above, the latter was the case.

The Committee accepted the sponsor's justification for not providing comparative bioavailability data on the 2.5 mg apixaban Phase III and commercial tablet formulations.

Quality Summary and Conclusions

Approval of the submission was recommended with respect to chemistry and manufacturing control.

With respect to bioavailability:

- There was a correlation between C_{max} and the amount dissolved in 30 minutes and this (in part) was used to justify the use of a disintegration test rather than a dissolution test.
- The PI reflects the results of the absolute bioavailability and food effect studies

III. Nonclinical Findings

Introduction

Apixaban is a new antithrombic agent for the prevention of venous thromboembolic events in patients with hip or knee replacement surgery. The nonclinical data package was comprehensive and included pharmacodynamics including mechanisms of action, pharmacokinetics in animals and *in vitro* and toxicology studies. The pivotal safety related studies were performed in compliance with Good Laboratory Practice. The range of studies was adequate to support the proposed use in humans.

Apixaban batches of different particle sizes were used in nonclinical studies but systemic exposures were determined in all pivotal toxicity studies.

Pharmacology

Pharmacodynamics

Anti-Xa activity

Apixaban is a reversible inhibitor of factor Xa with high selectivity. The anti-Xa and antithrombotic activities were demonstrated in *in vitro* assays and in animal species *in vivo*. *In vitro* assays using a synthetic tripeptide or prothrombin as the substrate and cofactors (factor Va, Ca^{2+} and phospholipids) revealed inhibition constant (K_i)values 0.6-0.7 nM at the physiological temperature (37°C), although lower K_i values were obtained at room temperature (0.41 nM) and without the cofactors (0.25 nM at 37°C and 0.08 nM at 25°C). The K_i for Xa was over 30,000 fold lower than for other proteolytic enzymes including several haemostatic factors (IXa, VIIa, XIa and thrombin). Apixaban maintains inhibitory activity to prothrombinase complex bound Xa (K_i 1.7 nM) or clot bound Xa (median inhibitory concentration [IC_{50}]1.3 nM). As a result of Xa inhibition, apixaban inhibits thrombin formation (IC_{50} 50-100 nM) in human platelet poor plasma and platelet aggregation (IC_{50} 3.5 nM) in platelet rich plasma.

Species difference in Xa inhibition was noted. The K_i values to Xa isolated from the rat, rabbit and dog were 1.4, 0.16 and 1.8 nM, respectively, compared to the human value of 0.08 nM at room temperature. There were also differences in the free fraction of apixaban

in plasma between animals and humans. Therefore, the pharmacodynamic study findings in animal species cannot be directly translated to humans.

In an *in vivo* study in rabbits, the Xa activity was dose dependently inhibited by apixaban at 0.01 to 1 mg/kg/h by IV infusion, with an approximate IC_{50} of 40 nM (or 18.4 ng/mL).

The major human metabolite, O-desmethyl apixaban sulfate, did not inhibit Xa activity at up to 20 μM *in vitro* (compared with clinical C_{max} 77 ng/mL or 0.167 μM), although inhibition was seen at higher concentrations (K_i 58 μM).

Effects on coagulation

Anticoagulation activities were observed in human plasma *in vitro*. The EC_{2x} (concentration doubling the coagulation time) was 1.9 μM (873 ng/mL) for prothrombin time (PT), 7.6 μM for activated partial thromboplastin time (APTT) and 0.19 μM in the HepTest (a proprietary test which measures heparin in human plasma). Prolonged PT and APTT were also evident in pharmacology and toxicology studies in animal species. As observed in the *in vitro* assays with human plasma, the effect on PT was greater than on APTT in animal studies. The EC_{2x} for PT was 7.6 μM in dogs, approximately 1.4 μM in rats, and 1.2 μM in rabbits.

Apixaban at up to 20 μM did not affect thrombin activity *in vitro* or in rabbits treated with apixaban at plasma concentrations up to 1.5 μM (690 ng/mL).

Effects on bleeding

Effects of apixaban on bleeding were investigated in animal studies. By IV infusion, bleeding time in various bleeding models was increased by 1.6-3x at plasma levels of 1.4 - 12 μM in rats (mesenteric bleeding model), by 1.3x at 3.7 μM in rabbits, and by 1.8x at 8-15 μM and by 5.2x at 32 μM in dogs. The plasma concentrations prolonging bleeding time are ≥ 6 fold higher than the antithrombotic IC_{50} values in rabbits and dogs but are similar to the antithrombotic IC_{50} values in rats (see below).

Antithrombosis

The antithrombotic activity of apixaban was demonstrated in several animal models of thrombosis. In venous, arterial or atrioventricular (AV) shunt thrombosis models in rats, rabbits and dogs, apixaban invariably inhibited thrombus formation with IC_{50} values (plasma apixaban concentrations) of 0.15-0.36 μM in rabbits, 1.4 μM in dogs and 1.8-7.6 μM in rats (Table 1).

Table 1: Antithrombotic IC_{50} values (plasma apixaban concentration in μM) and EC_x for PT and bleeding time in animal models of thrombosis

	AV-shunt	Venous thrombosis			Arterial thrombosis		EC_x §	
		Tissue factor induced	$FeCl_2$ induced	Silk thread induced	$FeCl_2$ induced	electric current induced	PT	Bleeding time
Rat	5.71	7.57	1.84	-	3.23	-	1.4 (2x)	5.0 (2.4x)*
Rabbit	0.357	-	-	0.146	-	0.106	1.2 (1.8x)	3.7 (1.3x)
Dog	1.4	-	-	-	-	1.2#	3.5 (1.6x)	7.6 (1.8x)

§ plasma concentrations that cause a significant prolongation of PT or bleeding time (fold increase relative to the control value in brackets); # plasma concentration doubling the time to blood vessel occlusion; * mesenteric bleeding time (1.03x for cuticle bleeding and 1.34x for renal cortex bleeding).

Apixaban also normalised the thrombotic markers, plasma thrombin-antithrombin III and soluble CD40 ligand levels, which are elevated in diabetic mice, at 5 and 50 mg/kg/day twice daily (bd) for the former and 50 mg/kg/day for the latter. Plasma apixaban concentrations were not measured in the study.

A pharmacodynamic study in rabbits showed that apixaban has an additive antithrombotic effect with aspirin or the aspirin and clopidogrel combination. The

apixaban and aspirin combination was more effective than apixaban or aspirin alone and the triple combination of apixaban, aspirin and clopidogrel was more effective than the dual combination of aspirin and clopidogrel. The thrombus weight was reduced by approximately 39% for the apixaban (0.04 mg/kg/h) and aspirin dual combination, compared to 20% for apixaban and 14% for aspirin alone. A 91% reduction in thrombus weight was measured for the apixaban (0.04 mg/kg/h), aspirin and clopidogrel triple combination, compared to 20% for apixaban and 56% for clopidogrel or the aspirin and clopidogrel combination. The same dose of apixaban did not significantly further prolong the increased bleeding time produced by aspirin alone or the aspirin and clopidogrel combination, although apixaban at a higher dose (2.1 mg/kg/h) increased bleeding time induced by aspirin or the aspirin and clopidogrel combination.

Secondary and safety pharmacology

A screening of receptor binding using the Novascreen assay (a proprietary assay for various pharmacological moieties) showed no significant binding of apixaban at up to 10 μM to 63 enzymes, receptors, and ion channels, indicating high selectivity of apixaban for Xa.

The effects on cardiovascular function were studied in dogs and in standard hERG and Purkinje fibre action potential assays *in vitro*. Apixaban or the O-desmethyl apixaban sulfate metabolite had no significant effects on hERG channels or action potentials in rabbit Purkinje fibres at up to 30 μM (13.8 μg/mL, compared to the clinical C_{max} of 77 ng/mL (free fraction 10 ng/mL) at 2.5 mg bd, suggesting that apixaban is unlikely to cause QT interval prolongation. No effects on blood pressure, heart rates or electrocardiogram (ECG) were observed in dogs following a single IV or oral (PO) dose of apixaban at plasma apixaban concentrations up to 8.75 μg/mL (approximately 70 times the clinical C_{max} of unbound apixaban). Blood pressure (BP) and ECG were unaffected in dogs following repeated PO administration for 12 months at C_{max} up to 11 μg/mL (approximately 92 times the clinical C_{max}) or IV dosing for up to 2 weeks at plasma apixaban concentrations 10-15 μg/mL at the time of ECG assessment (1-2 hours after dosing).

Dedicated central nervous system (CNS) or respiratory pharmacology safety studies were not submitted but neurological and respiratory examinations in the 2 week IV study and 3 month PO study in dogs revealed no abnormal neurological or respiratory findings. Respiration and arterial blood oxygen saturation were unaffected in the dog studies. Detailed neurological examinations were not described in the study reports. The following claim regarding the neurological assessment in the sponsor's *Nonclinical Pharmacology Summary* cannot be verified in the study reports:

Neurologic evaluations assessed mental state, gait, posture, cranial nerve function (assessed through menace response, pupillary light response, lid blink, eye retraction, gag reflex, eye position at rest, muscle palpation and tongue examination), and peripheral nerve function (muscle tone, spinal reflexes and postural reactions).

Nonetheless, high plasma apixaban concentrations were attained in the dog studies (up to 26 μg/mL by IV and 5.8 μg/mL PO). Body temperature was not affected by apixaban treatment.

No clinical signs indicative of neurological abnormalities were observed in the animal toxicity studies in rats or rabbits. Transient ataxia (lasting for 1-4 hours) was observed in mice shortly after an IV dose of apixaban at 25 or 50 mg/kg but not in rats at up to 25 mg/kg IV, with plasma concentrations > 141 μg/mL (>500 times the clinical C_{max}) based on the toxicokinetic data in the 2 week IV study. Tissue distribution studies in rats showed minimal distribution of drug related materials to the CNS. Apixaban is not expected to have clinically significant effects on CNS function.

In summary, safety pharmacology and repeat dose toxicity studies did not indicate potential hazards for cardiovascular, respiratory or CNS disturbance in patients.

Pharmacokinetics

Pharmacokinetic studies indicated that the animal species used in the pharmacology and toxicology studies were appropriate although there are differences in absorption, elimination and protein binding between animal species and humans. Adequate exposures were achieved in safety related nonclinical studies (see below).

Apixaban is poorly absorbed orally and a proprietary absorption enhancer (Labrafil M 1944 CS) was used in the oral formulations in the nonclinical studies. In addition, the active substance was milled to increase absorption. Labrafil increased oral absorption by sevenfold in rats compared to polyethylene glycol 400 (PEG400) or methylcellulose as the dose vehicle. Milling of the active substance increased the oral absorption by twofold in dogs. High plasma apixaban concentrations were achieved in toxicology studies in mice, rats, rabbits and dogs (see *Relative exposure* below). Following oral administration, peak plasma apixaban concentrations were reached in 1-4 hours in animals, compared to the human value of 3-4 hours (tablet formulation).

Binding of apixaban to plasma protein differs between species, ranging from approximately 50% in mice, 60% in cynomolgus monkeys and 63% in rabbits to 92% in dogs and 96% in rats, compared to 87% in human plasma. The distribution volume observed in a preliminary study was around 0.3 L/kg in rats and dogs, similar to the human steady state volume of distribution (V_{ss})(17-26 L, equivalent to 0.24-0.37 L/kg for a 70 kg person), indicating extravascular distribution. Distribution studies in rats with radiolabelled apixaban showed rapid and wide tissue distribution of apixaban derived material. High concentrations were detected in adrenal, gastrointestinal tract (GIT), liver, kidney, lungs, thyroid, skin and urinary bladder. Very low levels were detected in brain, testes and cardiac and skeletal muscle.

The metabolic pathways were similar in animal species and humans. Apixaban was primarily metabolised by O-demethylation to form a phenol derivative, O-desmethyl apixaban and further conjugation by sulfotransferase to O-desmethyl apixaban sulfate, the major metabolite in human plasma. Apixaban is also metabolised by hydroxylation, oxidation, opening of the keto-lactam ring via oxidation and hydrolysis of the amide moiety. The metabolism of apixaban is mainly catalysed by cytochrome P450 (CYP) 3A4/5, with minor contributions from 1A2, 2C8, 2C9, 2C19 and 2J2. The sulfation of O-desmethyl apixaban was mainly mediated by the SULT1A1*2 sulfotransferase.

The major human metabolite, O-desmethyl apixaban sulfate, was formed in laboratory animals although the concentrations varied between animal species. In rabbits, O-desmethyl apixaban sulfate accounted for 4-23% of total drug related material in plasma between 1 and 4 hours after an oral dose, comparable with the human values (2-16% between 1 and 6 hours). However, negligible amounts were detected in mouse, rat and dog plasma following oral administration (<1%). Since O-desmethyl apixaban sulfate is not pharmacologically active, the very small amounts of the metabolite formed in mice, rats and dogs do not detract the validity of the species as animal models for the investigation of potential toxicity of apixaban in humans. Because of the low oral bioavailability in rabbits due to rapid metabolism of apixaban to O-desmethyl apixaban and conjugates (sulfate and glucuronide) of the O-desmethyl moiety, apixaban was administered by the IV route (in addition to the PO route) in embryofetal development studies in this species, and effects on embryofetal development was also tested in mice in addition to the rat and rabbit (see *Reproductive toxicity* below).

Apixaban is eliminated by multiple pathways including metabolism, renal and biliary excretion. The elimination half-life ($t_{1/2}$) was in the range of 3-6 hours in rats and dogs after an oral dose, shorter than the clinical $t_{1/2}$ of 12 hours. There was evidence of excretion by the intestinal epithelium as shown by faecal recovery of unchanged drug and metabolites (25% of dose) in bile cannulated rats following IV administration. This is corroborated by the observation that apixaban is a substrate for P-glycoprotein (P-gp)(see *Pharmacokinetic interactions* below).

The majority of an oral dose was recovered in faeces (58-73% of dose) in mice, rats and dogs and around 10% of dose in urine, compared with 34% in faeces and approximately 23% in urine in human volunteers.

Pharmacokinetic interactions

In vitro studies with expressed CYP enzymes, human liver microsomes or human hepatocytes showed no significant inhibition or induction of CYP enzyme activities by apixaban. CYP3A4 is the major enzyme responsible for the metabolism of apixaban. The metabolism of apixaban was inhibited by CYP3A4 inhibitors (for example, ketoconazole) *in vitro*. Apixaban is also a substrate of P-gp and BCRP, but not a substrate of OCT and OATP transporters. Active transport of apixaban by P-gp was demonstrated in Caco-2 cells and LLC-PK cells expressing P-gp (efflux ratio: ~30) and transport in rat jejunum (efflux ratio: ~2). P-gp inhibitors (ketoconazole, cyclosporin A and naproxen) reduced apixaban efflux in cell monolayer assays *in vitro*. Similarly, active transport of apixaban was shown in BCRP-expressing MDCKII cell monolayers (efflux ratio: 8-30) and the efflux was inhibited by a BCRP inhibitor, Ko134. Although apixaban is eliminated by multiple pathways (renal, biliary and intestinal excretion and metabolism), strong CYP3A4 and P-gp inhibitors or inducers may alter plasma apixaban concentrations in humans.

The potential effects of apixaban on P-gp had not been adequately assessed. The sponsor stated that apixaban was not a P-gp inhibitor in its *Nonclinical Overview* and *Pharmacokinetic Written Summary* based on an *in vitro* Caco-2 cell assay. However, the integrity and P-gp function of the Caco-2 monolayer system in the study was not validated. In the Caco-2 cell assay described in study report 00102, no inhibition of P-gp mediated transport of apixaban was observed with LY-335979 (a P-gp inhibitor); nor did LY-335979 inhibit the transport of rhodamine 123, which is P-gp substrate. These findings contradict the results of two other studies which showed clear inhibition of P-gp mediated apixaban transport by two other P-gp inhibitors, ketoconazole and cyclosporin A. Therefore, the Caco-2 cell assay in the study report 00102 was not valid. In the sponsor's *Nonclinical Pharmacokinetic Written Summary*, the sponsor incorrectly referred the P-gp inhibition data to the *bd Study 300797734 (DCN 930017758*).

The sponsor addressed this deficiency by a new *in vitro* assay and reference to a clinical drug interaction study. In the new nonclinical study, apixaban showed no significant or dose dependent inhibition of P-gp activity. The transport of digoxin (5.3 μM), a model substrate of P-gp, was not significantly affected by apixaban at up to 50 μM. The sponsor also indicated that in a clinical interaction study (CV185028), apixaban (20 mg PO twice daily) did not alter the C_{max} and AUC of digoxin (0.25 mg PO daily). It can be concluded that apixaban is unlikely to inhibit the activity of P-gp in patients and thus affect the absorption or distribution of P-gp substrates.

Apixaban is not a substrate of organic anion or cation transporters and plasma concentrations of apixaban are unlikely to be affected by OAT or OCT inhibitors or inducers.

In a dog study, activated charcoal treatment decreased the area under the apixaban plasma concentration time curve from time zero to 24 hours ($AUC_{0\text{-}24h}$) by 24, 19 and 37%,

respectively, when charcoal was administered 0.25, 1 and 3 hours after the apixaban dose, suggesting that activated charcoal may be effective in the treatment of apixaban overdose in humans.

Relative exposures

Relative exposures are shown in Table 2.

Table 2: Relative exposures

Study	Species (route) [study no.]	Study duration (sampling time)	Dose (mg/kg/day)	$AUC_{0\text{-}24\ h}$ (µg.h/mL)	C_{max} (µg/mL)	Exposure ratio[a]	
						AUC	C_{max}
Repeat dose toxicity	Mouse (diet) [DN04099]	3 months (day 29)	1500	11.6	0.61	41	31
			3000	13.8	0.66	48	33
			4500	14.5	0.70	51	35
			6000	**15**	**0.79**	**52**	**40**
	Rat (diet) [DN04100]	3 months (day 85)	600	29.5	1.5	8	6
			1800	29.9	1.6	8	6
			2400	**37**	**1.95**	**10**	**8**
	Rat (gavage) [DN02043]	3 months (day 89)	75	7.11	1.37	2	6
			150	**11.4**	**1.59**	**3**	**6**
			300	11.3	1.40	3	6
	Rat (gavage)[b] [DN03118]	6 months (day 181)	50	21.5	3.0	6	12
			200	24.4	3.0	7	12
			600	35.0	4.2	10	17
	Dog (gavage) [DN03117]	12 months (day 360)	10	56	7.8	32	63
			30	**94**	**10.2**	**53**	**82**
			100	118	11.4	66	92
Carcino-genicity	Mouse (diet) [DN05068]	24 months (day 176)	150/150#	2.8/5.2	0.23/0.4	10/18	12/20
			500/500	5.1/10.4	0.31/0.6	18/36	16/30
			1500/3000	**7.3/16.8**	**0.37/0.89**	**26/59**	**19/45**
	Rat (diet) [DN05069]	24 months (day 384)	50	16.9	0.82	5	3
			200	27.2	1.28	8	5
			600	**27.9**	**1.35**	**8**	**5**
Fertility	Rat (gavage) [DN05056]	2 weeks before mating (day 10)	50	12.8/23.5#	1.63/2.57	4/7	7/10
			200	24.4/22.8	2.78/2.84	7/6	11/11
			600	**27.6/36.3**	**3.90/4.34**	**8/10**	**16/17**
Embryofetal development	Mouse (gavage) [DN06023]	GD 6-15 (GD15)	600	14.6	3.23	51	162
			900	17.5	2.54	61	127
			1500	**15.9**	**4.02**	**56**	**201**
	Rat (gavage) [DN03042]	GD 6-15 (GD15)	**3000[c]**	**42.7**	**7.2**	**12**	**29**
	Rabbit (gavage) [DN03045]	GD 7-19 (GD19)	**1500**	**0.355**	**0.025**	**0.9**	**0.9**
	Rabbit (IV) [DN05050]	GD 7-19 (GD19)	1.25	0.164	0.261	0.4	10
			2.5	0.393	0.566	1	21
			5	**0.954**	**1.28**	**2.5**	**47**
Pre/postnatal development	Rat (gavage) [DN08001]	GD 6-PPD 20 (PPD4)	**25**	**11.7**	**1.51**	**3**	**6**
			200	43.4	4.90	12	20
			1000	47.5	4.94	13	20

male/female values. NOAELs are bolded. GD, gestation day. PPD, post partum day. a, Adjusted for plasma protein binding. b, A NOAEL was not established in the 6-month study in rats, due to findings at all doses. c, NOAEL for embryofetal toxicity (NOAEL for maternal toxicity was 1000 mg/kg/day).

Animal:human exposure ratios are based on the steady state mean $AUC_{0\text{-}24h}$ of 1102 ng.h/mL and C_{max} 77 ng/mL in healthy human subjects at 2.5 mg bd. Because of the species differences in plasma protein binding (approximately 50% in mice, 96% in rats, 92% in dogs, 63% in rabbits, and 87% in humans), a factor of 0.5, 0.04, 0.08, 0.37 and 0.13 was applied to the mouse, rat, dog, rabbit and human C_{max} and AUC values, respectively.

Toxicology

General toxicity

The potential toxicity of apixaban was adequately investigated in animal studies. The dosing duration (up to 6 months in rats and 12 months in dogs) supports the long term use in humans, although the proposed indication was for short term use only. The oral gavage doses in the repeat dose toxicity studies produced plasma drug concentrations up to 52x (mouse), 10x (rat) and 66x (dog) the clinical exposure at 2.5 mg bd, based on AUC (free fraction). The No Observable Adverse Effect Level (NOAEL) is defined as no clinical or postmortem evidence of serious bleeding/haemorrhage and other changes not related to the pharmacological action of apixaban.

Single dose toxicity

No signs of toxicity were seen in mice or rats following a single oral gavage dose of apixaban at up to 4000 and 4510 mg/kg, respectively. There were no significant drug related findings in dogs at up to 1500 mg/kg/day PO. The particle size of apixaban used in the single dose oral studies was large. Based on toxicokinetic data from the 3 month oral gavage study in rats (C_{max} 1.40-1.59 at 150-300 mg/kg/day) and 1 year oral study in dogs (C_{max} 11.4 µg/mL at 100 mg/kg/day), in which animals were dosed with the same batch or a batch of similar particle size, plasma apixaban concentrations in the single dose toxicity studies in rats and dogs were at least 7x and 92x the clinical C_{max}. Deaths occurred in cynomolgus monkeys after an oral dose of apixaban at 100 or 300 mg/kg, probably due to bleeding at the blood collection site, a pharmacological effect of apixaban. Plasma C_{max} in these monkeys were 0.5-0.7 µg/mL (19-27x the clinical C_{max}).

The acute toxicity of apixaban by the IV route was studied in mice and rats. The only drug related findings were transient ataxia in mice shortly after dosing at 25 and 50 mg/kg, lasting 1-4 hours and one case of mortality in rats at 25 mg/kg. There were no toxicokinetic data in mice by the IV route. In rats, the plasma apixaban concentration 5 minutes following an IV dose of 12.5 mg/kg apixaban was 88-141 µg/mL, ~340-550x the clinical C_{max}.

Repeat dose toxicity

Apixaban was well tolerated in all animal species tested. The main finding in the repeat dose toxicity studies was prolonged coagulation (APTT and PT), a pharmacological action of apixaban. No serious bleeding was observed. Increased incidence and severity of discoloration at the injection and blood sampling site, suggesting haemorrhage was observed in treated animals in IV studies in rats, dogs and rabbits and some oral studies. Other salient findings are:

- plasma electrolytes alterations – decreased potassium and increased sodium and chloride in rats and dogs
- erythrophagocytosis and/or haemosiderosis in the mesenteric lymph node in rats

Decreased plasma potassium concentrations were frequently observed in rats and dogs dosed with apixaban by oral gavage, although the decreases were often not dose dependent or observed in both sexes. In rats, statistically significant decreases in plasma potassium concentration were detected in all oral gavage studies at various time points.

Potassium concentrations were also decreased in treated dogs, although often the difference compared to the vehicle controls was not significant. Associated with the decrease in potassium, sodium and chloride levels were generally increased. The changes in electrolytes were not worsened from continued apixaban treatment. On the contrary, the changes tended to subside after prolonged dosing. For example, the mean plasma potassium concentration in the high dose male rats was 9% lower than the vehicle control group at 4 weeks in the 6 month study and at 13 weeks the difference was only 3% and was not statistically significant.

Urinary electrolytes excretion was not measured in the toxicity studies. The cause of the changes in plasma electrolytes was unclear. However, the alterations in plasma electrolytes were not serious and the animals were clinically normal and showed no other abnormalities.

The number of rats with erythrophagocytosis and/or haemosiderosis of minimal severity in the mesenteric lymph node (but not the mandibular lymph node) was higher in all treated groups than in the control group of both sexes in the 6 month study with exposure ratios 6-10. Although the incidence was not dose dependent, it was clearly increased in all treated groups (14-15/20 compared with 3-5/20 in males and 12-16/20 compared with 3-8/20 in females). The same finding was only detected in the mandibular lymph node of one high dose male. No treatment related increase was observed in the dog studies or in the dietary studies in rodents.

Statistically significant decreases or increases in leukocyte counts and differentials were noted in the high dose group of short term studies in mice and rats. Since the changes were not consistent across studies and no significant increases or decreases were observed in the 6 month study in rats and 12 month study in dogs at high exposures (up to 10x in rats and 66x in dogs), the findings in the short term studies were most likely incidental.

High incidences of convulsions were observed in control and treated male mice in the carcinogenicity study. The incidence of convulsions was similar in treated and control groups (11, 14, 16, 21 and 12 at 0, 0, 150, 500 and 1500 mg/kg/day, respectively) but the number of episodes was higher in the treated groups without a dose relationship (32, 60, 143, 243 and 114 at 0, 0, 150, 500 and 1500 mg/kg/day, respectively) despite a 2.6 fold difference in exposure at the low and high doses. Very low incidences of convulsions were seen in female mice treated with apixaban (1 animal in the control and 150 mg/kg/day groups each, 3 animals at 500 mg/kg/day and none at 3000 mg/kg/day). A tissue distribution study in rats showed minimal distribution of apixaban or metabolites to the brain. Convulsions have also been reported in CD-1 mice in other laboratories (Rozmiarek 1999) and were considered to be related to frequent handling and possibly genetic predisposition.[6] Convulsions observed in the mouse carcinogenicity study with apixaban were probably not related to treatment.

High serum aspartate transferase (AST), alanine transferase (ALT) and sorbitol dehydrogenase (SDH) activities (1.4-10x the control group values) were observed in one low dose (600 mg/kg/day) female (died on Day 80) and one high dose (2400 mg/kg/day) female (euthanised) in the 3 month dietary study in rats, without significant hepatic lesions. Slightly increased serum ALT (2x) and gamma glutamyl transferase (GGT) (1.5x) in one male and alkaline phosphatase (ALP) (2x) in another male at 30 mg/kg/day PO were noted in the 2 week exploratory study in dogs. No increases were noted in other rat

[6] Rozmiarek H. Convulsions in rodents related to frequent handling. Lab Anim Sci 1999; 49: 468-469.

or dog studies or in mice at similar or higher doses and exposures. The incidences of increased serum transaminases were probably incidental findings.

Stomach lesions including minimal to moderate ulceration/erosion and/or epithelial hyperplasia, often with inflammation and subepithelial oedema were observed in the treated and vehicle control groups in the rat gavage studies with no difference between the vehicle control and treated groups. The stomach lesions subsided following recovery but squamous mucosal hyperplasia remained observable in some animals, with an additional lesion of subepithelial fibrosis, suggesting healing. The gastric lesions were related to the dose vehicle, Labrafil, which is derived from apricot kernel oil and was used as a solubility and bioavailability enhancer in nonclinical gavage studies. Since Labrafil is not used in the clinical formulation of apixaban, the gastric findings are not clinically relevant.

Genotoxicity

The genotoxicity of apixaban was adequately tested in bacteria and mammalian cells *in vitro* and in animals. Apixaban did not induce gene mutation in *Salmonella typhimurium* or chromosome aberration in Chinese hamster ovary cells *in vitro*. Negative results were returned from a micronucleus test in rats at up to 2000 mg/kg/day for 3 days and a lymphocyte chromosome aberration study in rats at up to 600 mg/kg/day for 30 days. The plasma apixaban C_{max} in the latter study was up to 14x the clinical C_{max}.

Carcinogenicity

The carcinogenic potential of apixaban was investigated in conventional long term studies in mice and rats. The doses and duration were appropriate. Apixaban was not carcinogenic in either species. Apixaban was administered in the diet at up to 3000 mg/kg/day in mice and 600 mg/kg/day in rats. The highest doses resulted in animal/human exposure ratios 42x (mouse) and 8x (rat) based on AUC and 32x (mouse) and 5x (rat) based on C_{max}. Higher doses could have been administered in the rat study but a 3 month dose selection study with an apixaban batch of larger particle size showed only a slight increase (by approximately 1.3 fold male and female combined) in exposure at doses from 600 to 2400 mg/kg/day. Furthermore, the plasma apixaban concentrations at 200 and 600 mg/kg/day in the carcinogenicity study with micronised apixaban (lower particle size 21.1) were comparable, suggesting saturation of absorption at high doses by the dietary route. Higher doses could have administered by oral gavage, although long term administration of the dose vehicle, Labrafil, induces stomach lesions in rats.

Reproductive toxicity

Effects on fertility and embryofetal and postnatal development were studied in rodents and rabbits by oral gavage or IV administration. In the fertility study in rats, treated males were mated with untreated females and treated females were mated with untreated males. Dosing started 2 weeks before mating and continued to gestation day (GD) 6. Fertility and early embryofetal development of male and female rats was unaffected at doses up to 600 mg/kg/day by gavage, with animal/human exposure ratios 8-10 (AUC) or 16-17 (C_{max}).

Studies on embryofetal effects were performed in mice, rats and rabbits. Rabbits were dosed by both the oral and IV routes because of the low exposure (0.9x the clinical exposure at 1500 mg/kg/day) by the oral route. The IV route yielded slightly higher exposure but the highest exposure was only 2.5x the clinical exposure based on AUC. Therefore, the mouse was also used in the embryofetal development studies. High exposures were achieved in pregnant mice and rats by oral gavage, and the animal/human exposure ratios at the high dose (1500 mg/kg/day in mice and 3000 mg/kg/day in rats)

were 56x and 12x, respectively. There was no evidence of effects on embryofetal development in the three animal species tested. No maternal toxicity was detected in mice or rabbits apart from prolonged coagulation. The only adverse maternal finding in rats was mucoid faeces at the high dose (3000 mg/kg/day). Pharmacokinetic analysis of fetal extracts or plasma showed very low placental transfer of apixaban. Apixaban concentrations in the fetus were 8-14% of the maternal plasma concentration in mice, 7% in rats and <1% in rabbits.

In a pre/postnatal study in rats at oral doses 25, 200 and 1000 mg/kg/day from GD 6 to postnatal day 20, mating indices were reduced in the offspring of the mid and high dose groups (79.2 and 73.9%, respectively, compared with 95.7% in the control group) at animal/human exposure ratios 12-13x and 20x at both doses, based on AUC and C_{max}, respectively. Fertility indices were decreased in the high dose group (65.2% compared with 95.7%). There were no treatment related effects at 25 mg/kg/day (exposure ratios: 3 and 6 based on AUC and C_{max}, respectively). High apixaban concentrations were detected in rat milk. The concentration of drug related substances (measured as radioactivity) in milk was 30x the maternal plasma levels, based on AUC. Over 96% of the radioactivity in milk was unchanged apixaban, indicating exposure of the rat pups to apixaban. The high apixaban concentrations in milk were probably related to the active transport of apixaban by the BCRP transporter. Apixaban was shown to be a substrate of BCRP (see discussion in *Pharmacokinetic interactions* above), which is expressed in mammary gland alveolar epithelial cells and secrets xenobiotic substrates to milk (Jonker et al. 2005; van Herwaarden et al. 2006).[7,8] Apixaban is most likely to be excreted in human milk.

Phototoxicity

A standard *in vitro* phototoxicity assay in 3T3 Balb/c mouse fibroblast cells showed no phototoxic effects at concentrations up to 35 µg/mL. The potential for phototoxicity in patients from the proposed clinical use is low.

Use in Children

Apixaban is not proposed for use in children. A dose range finding study in juvenile rats showed no overt toxicity but the study was a preliminary study without a full histological evaluation. Therefore, no conclusion can be made regarding the toxicological effects of apixaban in juvenile animals. The plasma apixaban concentrations in 10 day old rats (after 6 days of dosing) were 3 to7 fold higher than the plasma levels in weaning animals (21 days old). The main study was ongoing at the time of the submission. The sponsor should provide the study report for review in a future submission.

Nonclinical Summary and Conclusions

The nonclinical data package was comprehensive. The range of studies was adequate to support the proposed use in humans.

Apixaban is a factor Xa inhibitor. The anti-Xa and anti-thrombosis activities were demonstrated in nonclinical studies *in vitro* with human and animal Xa and in animal models of thrombosis. The dissociation constant K_i for human Xa with cofactors was 0.6-0.7 nM at 37°C and 0.41 nM at room temperature. The binding selectivity for Xa over other proteolytic enzymes was more than 30,000 fold. The major human metabolite, O-

[7] Jonker JW et al. The breast cancer resistance protein BCRP (ABCG2) concentrates drugs and carcinogenic xenotoxins into milk. Nature Medicine 2005; 11: 127-129.

[8] van Herwaarden AE et al. The function of breast cancer resistance protein in epithelial barriers, stem cells and milk secretion of drugs and xenotoxins. Trends in Pharmacological Sciences 2006; 27: 10-16.

desmethyl apixaban sulfate, at up to 20 μM did not inhibit human Xa activity, although inhibition was seen at higher concentrations (K_i 58 μM). Apixaban has an additive antithrombotic effect with aspirin or the aspirin and clopidogrel combination without prolonging bleeding time in rabbits at low doses.

Apixaban at the antithrombotic IC_{50} produced negligible prolongation of PT and bleeding time in rabbits and dogs, but it prolonged PT and bleeding times by $\geq$2x in rats.

Secondary and safety pharmacology studies did not raise issues of concern.

Apixaban is eliminated by multiple pathways including metabolism, renal and biliary excretion. There was also evidence of excretion by the intestinal epithelium. The major human metabolite, O-desmethyl apixaban sulfate, was formed in laboratory animals although the concentrations of the metabolite were low in most animal species. Since O-desmethyl apixaban sulfate is not pharmacologically active at clinically relevant concentrations, the animal species used in the nonclinical studies are appropriate. High exposures were obtained in toxicity studies. Species difference in plasma protein binding was noted and thus exposures in animals were compared with the human exposure based on the free fraction of apixaban.

Apixaban does not inhibit or induce CYP450 enzyme activities. CYP3A4 is the major enzyme responsible for the metabolism of apixaban. Apixaban is a substrate of P-gp and BCRP, but not a substrate of OCT and OATP transporters. The metabolism of apixaban and P-gp mediated transport was inhibited by CYP3A4 and P-gp inhibitors (for example, ketoconazole) *in vitro*. Similarly, the efflux of apixaban across BCRP expressing cell monolayers was inhibited by the BCRP inhibitor, Ko134. Although apixaban is eliminated by multiple pathways (renal, biliary and intestinal excretion and metabolism), strong CYP3A4 and P-gp inhibitors or inducers may alter plasma apixaban concentrations in humans. The potential effects of apixaban on P-gp had not initially been adequately assessed in nonclinical studies but this was addressed by the sponsor during the evaluation. Apixaban is unlikely to inhibit the activity of P-gp in patients and thus affect the absorption or distribution of P-gp substrates.

The potential toxicity of apixaban was adequately investigated in animal studies. The main finding in the single and repeat dose toxicity studies was slight prolongation of plasma coagulation parameters and haemorrhage at the site of injection or blood sampling, attributable to the pharmacological activity of apixaban. Other salient findings are alteration of plasma electrolytes (decreased potassium and increased sodium and chloride) in rats and dogs and erythrophagocytosis and/or haemosiderosis in the mesenteric lymph node in rats. The effects on plasma electrolytes were not always dose dependent and did not worsen with repeated long term dosing. It was recommended that clinical data be carefully reviewed for similar findings. Erythrophagocytosis and/or haemosiderosis of minimal severity were only detected in the mesenteric lymph node in rats. Similar findings were absent in dogs or in the mandibular lymph node in rats. This finding is probably not a serious risk in humans.

In vitro and *in vivo* studies showed no evidence of genotoxicity or carcinogenicity.

The only finding in reproductive studies was decreased mating and fertility in the offspring of rats treated with 200 or 1000 mg/kg/day apixaban (exposure margins: 12-13) from GD 6 to lactation day 20. No other findings were observed the fertility and embryofetal development studies in rats (fertility, embryofetal and postnatal development), mice (embryofetal development) and rabbits (embryofetal development). Apixaban was poorly transported across the placenta in all animal species but high milk concentration was detected in rats (milk/plasma ratio: 30).

An *in vitro* phototoxicity study showed no phototoxic potential.

A study in juvenile rats was ongoing at the time of the submission. The sponsor should provide the study report for review in a future submission.

There were no nonclinical objections to the approval of apixaban for the proposed clinical use.

IV. Clinical Findings

Introduction

The pharmacology of apixaban was evaluated in 26 pharmacokinetic (PK)/pharmacodynamic (PD) studies and 3 safety/efficacy studies. These included 3 bioequivalence/ bioavailability studies (CV185019; CV185020; CV185024), 11 studies evaluating drug-drug interactions (CV185002; CV185005; CV185015; CV185026; CV185028; CV185032; CV185033; CV185045; CV185054; CV185055; CV185060) and 7 studies in special populations (elderly: CV185022; ethnic groups: CV185013; CV185046: CV185058; renal impairment: CV185018; hepatic impairment: CV185025; and body weight: CV185059). Additional studies evaluated the effect on cardiac conduction (1 study: CV185031), patient populations (as part of 3 efficacy/safety studies: CV185010; CV185035; CV185047) and repeated dosing was also evaluated in study CV185002. A further 4 studies evaluated single dose PK and PD and included the effect of food on absorption (2 studies: CV185001; CV185008), sites of absorption from the GI tract (1 study: CV185007) and metabolism (1 study with radiolabelled drug: CV185006). Ascending intravenous doses of the drug were also evaluated in study CV185020.

Four key efficacy/safety studies were conducted in 11,828 subjects.

Two studies pivotal for this application were conducted mainly in Europe using the dose of enoxaparin (40 mg once daily [qd]) approved for both total knee replacement (TKR) and total hip replacement (THR) by the European Medicines Agency (EMA) and approved for THR by the US Food and Drug Administration (FDA).

- CV185047, a Phase III study in TKR
- CV185035, the largest of the Phase III studies in THR

Two other studies were conducted predominantly in North America and both used the same comparator enoxaparin dose (30 mg every 12 hours [q12h]) approved for TKR by the FDA.

- CV185010, a Phase II dose ranging study in TKR which identified the optimal dose of apixaban (2.5 mg bd) for the Phase III program
- CV185034, a Phase III study in TKR

These studies are considered supportive to this application because the comparator daily dose of enoxaparin was 50% higher than that used in EU and the rest of the world (ROW).

All four studies were robustly designed, international, multicentre, randomized, double blind, double dummy and active controlled. The study designs reflected the consensus opinion of clinical, health authority and regulatory guidelines for VTE prophylaxis.

The APPRAISE-2 (CV185068) study was available as a supplementary submission; this is a study of apixaban in acute coronary syndrome (ACS). This study was recently stopped by the Data Monitoring Committee because of excess bleeding and deaths with no significant efficacy benefit. Although the indication, apixaban dose and duration of treatment are

notably different from the prevention of VTE (VTEp) studies, the data are potentially relevant to the proposed product information.

The sponsors also submitted a safety update, specifically related to an apparent excess of amyotrophic lateral sclerosis (ALS) and Guillain-Barré syndrome (GBS) cases.

Pharmacokinetics

Introduction

A total of 814 mostly healthy subjects participated in Phase I studies; 716 received at least one dose of the drug. Apixaban was administered PO as single and multiple daily doses up to 50 mg and IV as single doses up to 5 mg. Duration of treatment was up to 10 days in some studies. Clinical pharmacology studies evaluated daily doses up to 50 mg, tenfold higher than the proposed clinical use. The majority of subjects were Caucasian (59%), male (82%) and < 65 years of age (93%) with an average body weight of 78 kg (range: 38 to 175 kg) and body mass index (BMI) of 26 kg/m^2 (range: 17 to 54 kg/m^2). Some specific studies were designed to evaluate pharmacokinetics (PK) in subjects with mild to severe renal impairment, mild to moderate hepatic impairment, older subjects (≥ 65 years of age), females, and under and overweight subjects. Further studies investigated the PK in Japanese and Chinese subjects.

Methods

Pharmacokinetic Data Analysis

The peak plasma concentration (C_{max}) and the time to reach the peak concentration (T_{max}) were obtained from experimental observations. The slope (λ) of the terminal phase of the plasma concentration time profile was determined with the weighting factor of 1 by the method of least squares (log-linear regression of at least three data points). The terminal half-life (t½) was estimated as ln2/λ. The area under the concentration time curve from time zero extrapolated to infinite time (AUC_{inf}) was determined by summing the areas from zero to the time of last measured concentration, calculated by using conventional trapezoidal and log-trapezoidal methods and the extrapolated area. The extrapolated area was determined by dividing the last measured concentration by the slope of the terminal log-linear phase. Total urinary recovery (UR_t) was calculated as the cumulative amount of drug excreted over 48 hours (h). UR_t of apixaban excreted was divided by the dose of apixaban and multiplied by 100 to obtain the percent of administered dose recovered in urine (%UR). Renal clearance (CLR) was calculated as: CLR = URt/$AUC_{(0-t)}$ (area under the concentration time curve from time zero to the last time of the last quantifiable concentration). Absolute oral bioavailability (F) using data from subjects treated with apixaban IV and PO, was calculated by obtaining the dose normalized AUC_{inf} ratio of PO divided by IV and multiplying the ratio by 100. Total plasma clearance (CL) was calculated as: CL = Dose/ AUC_{inf} for IV only. Steady state volume of distribution (Vss) was calculated as: Vss = Dose • MRT / AUC_{inf} for IV only, where MRT (mean residence time) is the ratio of area under the moment curve (AUMC) over area under the curve (AUC). The AUC ratio was adjusted for molecular weight differences between the M1 metabolite and apixaban.

Statistical Analysis

All statistical analyses were carried out using SAS/STAT Version 8.2. Geometric means and coefficients of variation were provided for C_{max}, AUC_{inf}, $AUC_{(0-t)}$, AUC ratio and dose normalized F. Medians and ranges were presented for T_{max}. Means and standard deviations were provided for other pharmacokinetic parameters. To assess the dependency on dose, scatter plots of apixaban C_{max}, AUC_{inf}, and $AUC_{(0-t)}$ versus dose were provided where appropriate. Additionally, scatter plots of apixaban CL, CLR, Vss, and %UR versus dose were also provided where appropriate.

Absorption

Bioavailability

Absolute bioavailability of apixaban was investigated in a randomized, double blind, placebo controlled, sequential, ascending single IV dose study. Apixaban PK were characterized by dose proportional increases in systemic exposure (as determined by AUC_{inf}). Mean values across dose panels for volume of distribution (Vss) and total clearance (CLT) ranged from 17 - 26 L and 3.2 - 3.5 L/h, respectively. Across dose panels renal clearance was 0.61 - 1.10 L/h and accounted for approximately 17% - 30% of CLT. The Vss was similar to the estimated volume of extracellular fluid (18 L in a 70 kg man), suggesting limited intracellular distribution. Both CLT and Vss were similar across the dose range tested. Oral administration resulted in a multiphasic decline in plasma concentration similar to that observed with IV administration. The $t_{½}$ observed following PO administration was longer than that observed following IV administration resulting in comparable exposure (10.8 h vs 5.6 to 8.4 h). Following PO administration mean bioavailability was 66% (individual subject range: 51% to 86%).

However, in the drug interaction study with rifampin (**CV185045),** dose adjusted apixaban absolute bioavailability (F) values were 49% for apixaban alone and 37% for apixaban in the presence of rifampin. Absolute bioavailability of apixaban was reduced by approximately 25% when apixaban was given with rifampin. This study was discussed briefly in *Section II* and in more detail later.

Bioequivalence

A bioequivalence study was conducted to evaluate the effect of modifications of tablet composition and manufacturing process on the *in vitro* dissolution and *in vivo* bioavailability at a 20 mg dose (**CV185019**). This study was discussed briefly in *Section II.* Results of this study demonstrated that the Phase III prototype tablets (coated wet granulation and coated dry granulation) were bioequivalent to the Phase II uncoated wet granulation tablets. The dry granulation prototype was selected for manufacturing and testing in Phase III clinical trials. To further understand the performance of the Phase II wet granulation tablet with respect to the Phase III dry granulation tablet and the potential influence of tablet dissolution rate on *in vivo* exposure, an additional comparative bioavailability study (**CV185024**) was conducted at a 5 mg dose (2x2.5 mg tablets). This study was also discussed briefly in *Section II.* Three types of tablets (A, B and C) with different dissolution rates were investigated. The results demonstrated that, for tablets with similar dissolution rates, C_{max} and AUC of the coated Phase III tablet relative to the uncoated Phase II tablet, met bioequivalence criteria. Tablets with different dissolution rates had similar AUCs, but did not meet equivalence criteria for C_{max}. The lower boundary of the 90% confidence interval of ratio of geometric mean C_{max} was 0.788. Data from the relative bioavailability study (**CV185024**) at the 5 mg dose and the bioequivalence study (**CV185019**) at the 20 mg dose showed comparable exposure between tablets manufactured by wet to dry granulation process, despite the fact that the 20 mg dose was outside the dose linearity range shown for the tablet formulation.

Two tablet strengths, 2.5 mg and 5 mg, were selected for Phase III studies. For the current application only the 2.5 mg formulation is being proposed for commercial release. There were differences between the commercial and the clinical tablet formulations with respect to their film coat colour, weight of film coat and lactose/HPMC (hydroxypropyl methylcellulose) ratio. It was established through dissolution testing that these changes were minor and do not affect the release of apixaban from the drug product. Nevertheless there is no *in vivo* study to establish bioequivalence between the proposed commercial formulation and that used in the clinical development program.

Influence of Food

The effect of a high fat breakfast consumed 5 minutes (min) before administration of Phase II tablet of apixaban was investigated in 6 healthy subjects in a nonrandomized, single sequence assessment of the effect of food on the PK of apixaban (**CV185001**). Both T_{max} and C_{max} were affected by food consumption; apixaban geometric mean AUC_{inf} and $AUC_{(0-t)}$ were 46% and 43% greater than in the fasted state. The small sample size (N=6) and limitations associated with a sequential study design precluded a firm conclusion about the effect of food on apixaban PKs.

A further food effect study (**CV185008**) was conducted using Phase II tablets and a dose of 10 mg administered as 2 x 5 mg tablets. The study was conducted as a randomized, open label, single dose, crossover study in healthy subjects. This study was discussed briefly in *Section II*. Apixaban was administered in both the fasted state and within 5 minutes of a standard high fat, high calorie meal. The 10 mg total dose tested in this study represents the highest dose evaluated in Phase III clinical trials, while the proposed dose strength was 5 mg. In this study, food had no significant effect on the C_{max} and AUC_{inf} of apixaban. The 90% confidence intervals (CI) of C_{max}, (1.004, 1.197), AUC_{inf} (1.004, 1.086), and $AUC_{(0-t)}$ (1.002, 1.099) were completely contained within 80% to 125%, indicating the absence of a significant effect of a high fat, high calorie meal on the PK of apixaban. The median T_{max} value was 3 h when fasted and 4 h following administration of 10 mg apixaban with a high fat meal. This minimal increase in T_{max} likely reflects delayed gastric emptying following the high fat meal. Mean values for half-life in the fed and fasted states were similar. The study demonstrates that a high fat, high calorie meal does not have a significant effect on the PK of apixaban. Apixaban can thus be administered either in the fasted state or following a meal. The Phase III studies were subsequently conducted allowing administration of apixaban without regard to meal times.

Sites of Absorption in Gastrointestinal Tract

A randomized, open label, four period crossover study to assess the extent of absorption of apixaban when delivered as a solution to specific regions in the gastrointestinal (GI) tract was performed in healthy subjects (**CV185007**). Systemic exposure decreased in the order of Treatment A, B, C and D. Based upon C_{max}, $AUC_{(0-t)}$, and AUC_{inf}, the apixaban exposure resulting from solution dosing to distal small bowel (Treatment B) was approximately 40% of that from oral solution dosing (Treatment A). Exposure from solution dosing to ascending colon (Treatment C) was 10-20% of that from oral solution dosing. A crushed tablet delivered to the ascending colon (Treatment D) resulted in exposure approximately 40% of that from solution dosing to the same region (Treatment C). Apixaban appeared to exhibit region dependent absorption when administered as a solution, with decreased absorption at more distal sites in the GI tract.

Distribution

The apixaban plasma concentration time profile after a single IV bolus dose was characterized by a rapid decline within the first 30 minutes post dose followed by multiphasic disposition; a similar multiphasic profile was observed following PO administration. Following an IV bolus dose, mean steady state volume of distribution for apixaban was ~ 21 L based on non-compartmental PK analysis, suggesting a low degree of tissue distribution. In human serum, *in vitro* protein binding was 87%. *In vitro*, binding of apixaban to α1-acid glycoprotein (9%) was low and less than its degree of binding to human serum albumin (66%). Protein binding was ~93% in healthy subjects and subjects with mild to moderate hepatic impairment suggesting protein binding was not altered by mild or moderate hepatic impairment (**CV185025**). The blood: plasma ratio of apixaban

observed in the human ADME study (~ 0.75) was close to 1 indicating that apixaban and its metabolites do not preferentially distribute into red blood cells.

Elimination

Excretion

Apixaban is eliminated by multiple pathways including metabolism, renal clearance and biliary clearance. From observed data, faecal (52%) and urinary recovery (24%) of apixaban and its metabolites account for the majority of the administered dose.

Metabolism

Metabolites identified in humans were found in other species; there were no unique human metabolites. After oral administration, apixaban is the major drug related component in the circulation and undergoes both phase 1 and phase 2 metabolism. Metabolites account for ~ 25% of the recovered dose following administration of 20 mg [^{14}C]apixaban to healthy subjects. Routes of metabolism included O-demethylation (to O-desmethyl apixaban), O-demethylation with sulphation (to O-desmethyl apixaban sulphate), mono-oxidation (to hydroxyapixaban and 3-hydroxyapixaban), O-demethylation with hydroxylation (to hydroxyl-O-desmethyl-apixaban-2) and O-demethylation with hydroxylation and sulphation (to hydroxylated O-desmethyl apixaban sulphate-1). The primary metabolic pathway in humans appears to be O-demethylation to form the phenol derivative, followed by sulphation to form the O-desmethyl apixaban sulphate. O-desmethyl apixaban sulphate was the predominant circulating metabolite; based on the area under the plasma concentration time curve from zero to 48 hours ($AUC_{(0\text{-}48\ h)}$), exposure to O-desmethyl apixaban sulphate was ~25% of the exposure to apixaban in healthy subjects with a plasma disappearance rate similar to parent. Only ~5% of the administered dose was recovered as this metabolite, indicating that the metabolite has a more limited volume of distribution than the parent. Minor plasma metabolites (each < 1% of plasma radioactivity at each time point) included O-desmethyl apixaban, 3-hydroxyapixaban, and hydroxylated O-desmethyl apixaban sulphate-1. While O-desmethyl apixaban sulphate is the major human circulating metabolite, it does not have meaningful pharmacological activity.

The *in vitro* formation of O-desmethyl apixaban was primarily mediated by CYP3A4 and 3A5 with relatively minor contributions of CYP1A2 and CYP2J2; a low level of formation was catalysed by CYP2C8, CYP2C9 and CYP2C19. Sulphate conjugation was mediated primarily by SULT1A1*2 with minor activity observed for SULT1A3, SULT1E1, and SULT2A1. Apixaban exhibits linear PK with no evidence for saturable metabolism.

Pharmacokinetics of metabolites

An inactive metabolite, BMS-730823 (M1, O-desmethyl apixaban sulfate), is the main circulating metabolite of apixaban present at approximately 25% of parent $AUC_{(0\text{-}48)}$ (**CV185020**). The PK of the metabolite was assessed in five studies. Following IV and PO apixaban administration the PK of M1 was similar to that of the parent drug (**CV185020)**. Peak plasma concentrations were achieved about 4 h after that of apixaban. Following IV administration, $t_{½}$, CLR, and apixaban to metabolite ratio (MR) were consistent across the dose range. Proportional increases in AUC were observed relative to the dose of apixaban. This suggests that metabolite formation is not saturated over the dose range tested (0.5 to 5 mg).

In subjects with renal impairment, M1 exposure was increased compared to those with normal renal function (**CV185018**). A regression analysis vs 24 h creatinine clearance (CLcr) for this inactive metabolite showed that subjects with mild (24 h CLcr=65 mL/min), moderate (24 h CLcr=40 mL/min) and severe (24 h CLcr=25 mL/min) renal impairment,

respectively, had 17%, 31%, and 40% higher geometric mean C_{max}, and 0.5, 2 and 2.4 fold higher geometric mean AUC_{inf} compared to subjects with normal renal function (24 h CLcr=100 mL/min). In subjects with severe impairment of renal function (24 h CLcr ≤15 mL/min) the metabolite AUC was estimated to be 2.7 fold higher than in subjects with normal renal function.

An ascending dose study was performed in 16 healthy Japanese and Caucasian males randomized to oral apixaban or placebo in a 3:1 ratio (**CV185013**). The appearance rate for M1 in plasma was similar between Japanese and Caucasian subjects. Plasma concentrations of M1 were lower in Japanese than in Caucasians during the disposition phase. The terminal slope of apixaban was parallel to that of M1 in both ethnic groups. Elimination of apixaban and M1 appeared to be faster in Japanese than in Caucasians. M1 plasma concentrations peaked at about 8 hours post dose in both ethnic groups and their C_{max} values were similar. As was observed for the parent drug, the mean $AUC_{(0-t)}$ values for this metabolite were about 10-20% lower in Japanese than in Caucasian subjects. CLR, %UR and metabolite to apixaban AUC ratios were similar between the two ethnic groups across all dose panels**.**

An ascending multiple dose study was performed in healthy male Japanese subjects (**CV185046)**. The appearance of M1 in plasma lagged behind that of apixaban by about 2 to 4 hours. The terminal slope of M1 appeared to be parallel to that of apixaban. M1 trough concentrations (C_{min}) did not change appreciably beyond 72 h at all dose levels, indicating that steady state conditions were achieved by Day 4. A moderate accumulation of M1 was observed from Day 1 to Day 7, as shown by accumulation index values of 2 to 3. The Day 7 values for T_{max}, CLr and the M1 to apixaban AUC ratio (approximately 25%) were similar across all doses. M1 renal clearance remained unchanged after multiple days of bd dosing.

The effect of apixaban on the QT/QTc interval was investigated in 40 healthy volunteers (**CV185031**). There were less than dose proportional increases in C_{max} and the area under the concentration time curve in one dosing interval (AUCτ) for both apixaban and M1. Plasma concentrations of apixaban were similar at pre-dose and 24 h post dose on Day 3. Median apixaban T_{max} values for apixaban 10 mg and 50 mg doses were similar (4 h and 3 h, respectively).

Dose proportionality and time dependency

Dose proportionality

Dose proportionality for apixaban was examined in **CV185013**, in which healthy Caucasian and Japanese subjects each received 4 single oral doses of apixaban tablets from 2.5 mg to 50 mg, in ascending order. Increases in exposure were in proportion to the dose increment for doses up to 10 mg. As evident by the regression analysis, dose proportionality was not maintained over the full dose range (2.5 to 50 mg). Point estimates and 95% confidence intervals for the dose proportionality parameter were <1.0 for each PK parameter. The divergence from linearity became greater as the dose increased, suggesting a dissolution limiting effect. For the oral solution, apixaban exposure increased in proportion with increasing doses up to the highest dose tested, 20 mg, confirming that the less than dose proportional increase with tablet formulations was most likely due to dissolution rate limited absorption at doses ≥ 25 mg. Loss of proportionality at doses ≥ 25 mg is unlikely to be clinically important as the loss of proportionality occurs at a tenfold higher dose than that proposed for use in the current indication.

Forty subjects were assigned to apixaban in 1 of 5 dose panels (**CV185020**). Apixaban AUC_{inf} increased in proportion to increases in IV dose from 0.5 to 5 mg, as demonstrated by dose ratios of 1:2.5:5:7.5:10 and corresponding AUC_{inf} ratios of 1:2.5:4.9:7.9:9.7.

Clearance, Vss, CLR, and %UR were relatively consistent across dose groups. Apixaban exhibits linear PK within the proposed range of doses to be used therapeutically.

Time dependency

A randomized, sequential, ascending multiple dose study was performed in eight healthy Japanese male subjects (**CV185046**). Increases in apixaban exposure as measured by AUCτ were approximately proportional to increases in dose increment. Following multiple daily doses of apixaban, C_{min} values did not change appreciably beyond 48 h at all dose levels, indicating that steady state conditions were achieved by Day 3. A modest and similar degree of accumulation was observed for all doses, as shown by accumulation index values of 1.7 to 2.0. Elimination half life after 7 days of dosing ranged from 8 to 10 hours. Apixaban PKs are time independent; single dose data predict multiple dose PKs.

Intra- and inter-individual variability

In healthy subjects, within-subject variability of apixaban is low (~20% coefficient of variation [CV]), as is the between-subject variability (~30% CV) for C_{max} and AUC parameters and both are independent of dose. Inter-individual variability in PK parameters is slightly higher in patients (~40% CV).

Pharmacokinetics in target population

Population PK (PPK) and exposure response analyses, incorporating data from Phase I and Phase II/III studies, were also conducted. The PPK analysis for apixaban was conducted with a total of 11252 observations of plasma concentration from 1284 subjects. Data from advanced cancer subjects was included to improve the PPK analysis by providing a population of subjects with similar demographic characteristics to TKR and THR surgery subjects but who did not undergo orthopaedic surgery. Apixaban exposure was characterized by a two compartment model with first order absorption and elimination. The model was parameterized in terms of rate of absorption (KA), apparent clearance (CL/F), apparent volume of distribution of the central compartment (Vc/F), apparent inter-compartmental clearance (Q/F), and apparent volume of distribution of the peripheral compartment (Vp/F). The effect of calculated creatinine clearance (cCrCL) on the CL/F of apixaban was incorporated into the model. A subject with a cCrCL of 20 mL/min would be predicted to have a 27% reduction in CL/F relative to a subject with a cCrCL of 80 mL/min. Analysis of the other covariate effects in the PPK model revealed that the effects of age, sex and surgery were statistically significant for apixaban CL/F. The CL/F was reduced by 26% relative to non-surgery subjects in the 3 days immediately following TKR and THR surgery. After the first 3 days the CL/F is reduced by only 11%. Female subjects are predicted to have an 11% reduction in CL/F. Age alone plays a relatively minor role in the CL/F, as a 75 year old subject would be expected to have a reduction in CL/F of only 11% relative to a 30 year old subject. The effects of body weight and haematocrit were significant for Vc/F. The PPK model predicts total plasma CL/F for a 30 year old male healthy volunteer with a cCrCL of 80 mL/min and a body weight of 80 kg to be 4.29 L/hr. Alternatively, a male TKR or THR surgery subject with an age of 75 years, a cCrCL of 80 mL/min and a body weight of 80 kg would be predicted to have a plasma CL/F of 3.37 L/hr. The final PPK model was used to predict the range of exposures to be expected in TKR and THR surgery subjects following administration of the 2.5 mg bd dose regimen. The accumulation ratio of apixaban would be ~ 1.6.

Special populations

Age and Gender

The effect of age and gender on apixaban PK was examined in an open label, single dose, 2 x 2 factorial designed study of 20 mg apixaban (**CV185022**). C_{max} by age met the pre-

specified equivalence criteria. The 90% CI were outside the pre-specified 80% to 125% no effect criterion for AUC_{inf} by age and C_{max} and AUC_{inf} by gender. Older age was associated with a 32% higher apixaban AUC_{inf}. Female gender was associated with an 18% and 15% higher C_{max} and AUC_{inf}. The effects of age and gender were independent of each other. The potential relationship between apixaban exposures versus Cockcroft-Gault (C-G) estimated creatinine clearance (CLcr), body weight, and body mass index were explored. These analyses suggest that differences in C-G estimated CLcr may have played a role in the observed differences, as apixaban plasma concentration was inversely related to estimated CLcr. The differences observed are not expected to result in a clinically relevant effect for apixaban.

Single and multiple dose PK of apixaban were assessed in eighteen Chinese subjects (12 males and 6 females) randomly assigned in a 2:1 ratio to receive apixaban or matched placebo (**CV185058)**. Apixaban T_{max} and $t_{½}$ remained relatively unchanged following single and multiple dose administration and appear to be comparable between male and female subjects. Peak concentrations were observed at around 3 h and mean terminal $t_{½}$ was approximately 11 h. The accumulation index at steady state was approximately 1.7. After single dose administration, exposure appeared to be higher in female subjects (N=4) by 29%, 39% and 39% for C_{max}, $AUC_{(0-t)}$ and AUC_{inf}, respectively. After multiple dose administration, exposure appeared to be higher in female subjects (N=4) by 36% and 41% for C_{max} and AUCτ, respectively. CLR in male subjects (N=8) appeared to be modestly higher than that in female subjects, although a greater percentage of the dose of apixaban was excreted unchanged in the urine of females compared to males. Following multiple doses of apixaban, C_{min} values did not change appreciably beyond Day 7, indicating that steady state conditions were achieved by the third day. Apixaban demonstrated a modest degree of fluctuation consistent with its half-life and frequency of administration.

Body Weight

In an open label, single dose, parallel group study the PK of apixaban was investigated in 55 subjects in 1 of 3 weight groups: ≤ 50 kg (low weight), 65 to 85 kg (reference weight) and ≥ 120 kg (high weight) (**CV185059**). Apixaban T_{max} was similar in all weight groups. The plasma elimination $t_{½}$ was higher for ≤ 50 kg group and was lower for ≥ 120 kg group as compared to the reference body weight group. Plasma concentrations from subjects in the ≥ 120 kg group often fell below the lower limit of quantification (LLOQ) after 48 h, hence the shorter $t_{½}$ value reported may not accurately reflect the terminal elimination phase. The apixaban urinary excretion and renal clearance did not show any trend towards change with extremes of body weight. The VSS/F and CLT/F exhibited a modest increase for the high body weight subjects and a modest decrease for the low body weight subjects, as compared to the reference body weight group. For apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$, 90% CIs for the ratios of geometric means (versus reference) were calculated separately for the ≤ 50 kg and ≥ 120 kg body weight groups. For subjects in the low weight group, apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$ were 27%, 20% and 19% higher, respectively, compared to the reference weight group. For subjects in the high weight group, the geometric means for apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$ were 31%, 23%, and 23% lower, respectively, compared to subjects in the reference weight group. The 90% CI exceeded the pre-specified no effect criteria for these comparisons. Because the low body weight group was predominately (89%) female and the high body weight group was predominately (84%) male, it is possible that the differences could be related to gender rather than weight. Scatter plots for both individual C_{max} and AUC_{inf} normalized by dose and body weight indicated similar exposure in males and females within each body weight group, suggesting lack of gender influence. A direct, linear relationship between plasma anti-Xa activity and apixaban plasma concentration was observed, regardless of body weight. There were trends towards decreasing plasma anti-Xa activity with increasing

body weight that were attributed to the observed differences in plasma concentration. Overall, in the case of low and high body weight, the differences in apixaban C_{max} and AUC were within 30% and 20% of the reference group, respectively. The modest influence of weight on apixaban PK is consistent with its low volume of distribution and clearance. These data indicate that the effect of extreme body weight is unlikely to require dose adjustment.

Race

Clinical pharmacology data were derived primarily from Caucasian subjects (59%), followed by Black (28%), Asian (10%) and other races (2%). The impact of race (or ethnicity) on apixaban PK has been evaluated in three Phase I studies involving Japanese, Chinese and Caucasian subjects.

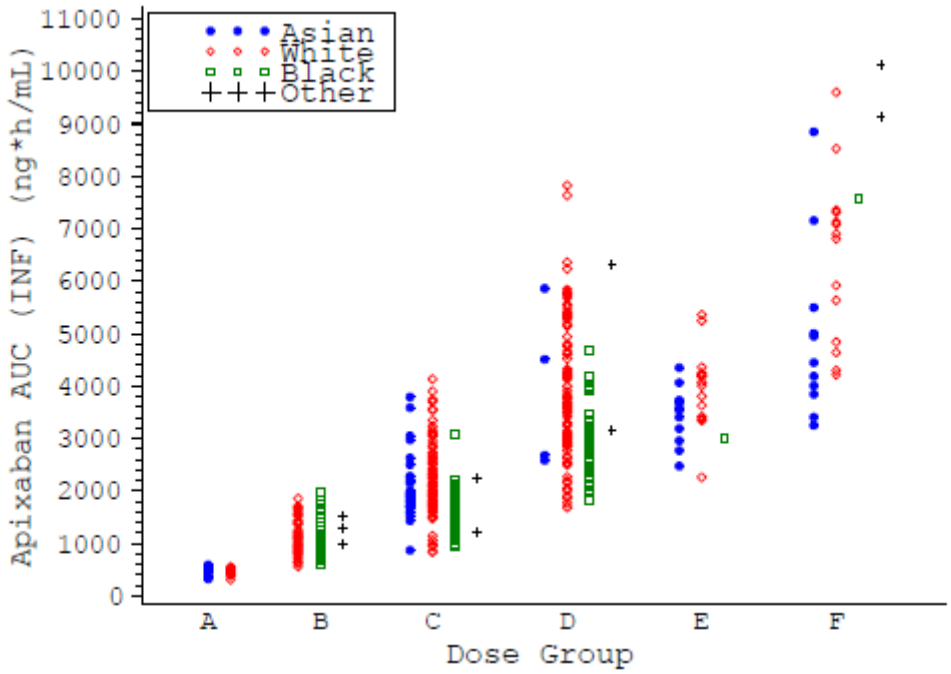
An ascending dose study was performed in 16 healthy Japanese and Caucasian males randomized to oral apixaban or placebo in a 3:1 ratio (**CV185013**). The point estimates and 90% CI for the Japanese to Caucasian ratios for C_{max}, AUC_{inf} and $AUC_{(0-t)}$ are consistent with no ethnic differences since the estimates were generally close to 1.0 and CIs generally included 1.0. When point estimates and CIs did not include 1.0 apparent exposure in Japanese subjects was within about 20% of that observed in Caucasian subjects. Exposure increased proportionally with doses up to 10 mg and less than proportionally with higher doses. Apixaban PK was consistent between Japanese and Caucasian subjects. There was evidence demonstrating that apixaban PK were linear and proportional across a fourfold dose range.

An ascending multiple dose study was performed in healthy male Japanese subjects (**CV185046**). Increases in apixaban exposure were approximately proportional to increases in dose. Following multiple daily doses C_{min} values did not change appreciably beyond 48 h at all dose levels, indicating that steady state was achieved by Day 3. A modest and similar degree of accumulation was observed for all doses, as shown by an accumulation index of 1.7 to 2.0. Apixaban $t_{½}$ after 7 days of dosing ranged from 8 to 10 h. The multiple dose PK profile observed was consistent with that in other studies (for example **CV185002A**) and with the single dose profiles observed in Japanese and Caucasian subjects (**CV185013**).

A placebo controlled, double blind, single sequence, single and multiple dose study was conducted in 18 (12 male, 6 female) healthy Chinese subjects randomized to receive apixaban or matched placebo in a 3:1 ratio (**CV185058**). Apixaban single dose PK parameters were similar to previous studies. Intersubject variability for C_{max} and AUC parameters was low with CVs ≤ 30% after single or multiple doses. Apixaban C_{max} and AUCτ were slightly higher in the 4 female subjects relative to the 8 male subjects (36% and 41%, respectively). The apixaban T_{max} and $t_{½}$ of approximately 3 and 11 h, respectively, were relatively unchanged after single or multiple dose administration and were comparable between males and females; the observed accumulation at steady state (~ 1.7) was consistent with the ~11 h $t_{½}$ and frequency of administration.

Results of the three studies involving Japanese, Chinese, and Caucasian subjects indicated that the PK (and PD) profile were comparable regardless of race. This is further illustrated by the relationship between AUC_{inf} by race and dose shown in Figure 1. In addition, Asian race and African American race were not found to be significant predictors of apixaban CLT/F or Vss/F in the population PK analysis.

Figure 1: Apixaban AUC_{inf} by Dose and Race



Dose groups: A: 2.5 mg; B: 5 mg; C: 10 mg; D: 20 mg; E: 25 mg; F: 50 mg

Impaired Renal Function

An open label, single dose cohort study investigated the effect of renal impairment on apixaban PK (**CV185018).** Apixaban AUC_{inf} generally increased and became more variable with decreasing CLcr (Table 3).

Table 3: Pharmacokinetic Parameters of Apixaban in Renal Impairment

Renal Function Group	Apixaban Pharmacokinetic Parameters							
	Cmax (ng/mL)	Tmax (h)	AUC (INF) (ng·h/mL)	AUC (0-T) (ng·h/mL)	T-HALF (h)	CLT/F (mL/min)	CLR (mL/min)	%UR (%)
Normal (n = 8)	224 (25)	2.75 (2 - 4)	2528 (26)	2469 (27)	15.1 (7.6)	65.9 (20)	6.83 (33)	10.42 (2.66)
Mild (n = 10)	229 (33)	4 (1 - 6)	3288 (37)	3226 (38)	14.6 (7.3)	50.7 (34)	3.81 (53)	9.36 (6.23)
Moderate (n = 7)	288 (18)	4 (3.1 - 4)	4479 (23)	4387 (23)	17.6 (6.0)	37.2 (21)	1.94 (89)	7.18 (6.53)
Severe (n = 7)	210 (37)	4 (3 - 4)	3221 (49)	3115 (49)	17.3 (7.4)	51.7 (69)	1.94 (45)	4.65 (3.34)

Note: Results are presented as geometric mean (%CV) except for Tmax which is presented as median (min-max) and T-HALF and %UR which are presented as mean (SD).

In contrast, the relationship between apixaban C_{max} and 24 h CLcr was less evident. The relationship between 24 hr CLcr and apixaban AUC_{inf} was assessed by linear regression. Regression model based point estimates and 90% CI of the ratios of apixaban AUC_{inf} geometric means (impaired versus normal) were computed separately for each of the three renal function groups (B, C, and D). The midpoints of the standard CLcr ranges for mild (65 mL/min, 50 to 80 mL/min), moderate (40 mL/min, ≥30 to <50 mL/min), and severe (15 mL/min, <30 mL/min) renal impairment as well as a value approximating the

midpoint of the severe range based on observed data (25 mL/min, 15.7 - 28.0 mL/min) were selected for comparison with a representative value for normal renal function (100 mL/min). Similar analyses were conducted to relate apixaban $AUC_{(0-t)}$ and C_{max} to 24 hr CLcr, and BMS-730823 AUC_{inf}, $AUC_{(0-t)}$ and C_{max} to 24 hr CLcr. The association between AUC_{inf}, and 24 hr CLcr was re-expressed as a relationship between CLT/F and 24 hr CLcr for apixaban. Additionally, the relationships between apixaban C_{max}, AUC_{inf}, and $AUC_{(0-t)}$ versus iohexol CLT and CLcr estimated by Cockcroft-Gault and MDRD equations were assessed by generating scatter plots of the CLcr estimates versus exposure parameters. Based on the regression model, subjects with mild (24 hr CLcr=65 mL/min), moderate (24 hr CLcr=40 mL/min), and severe (24 hr CLcr=25 mL/min) renal impairment had geometric mean C_{max} values similar to the normal renal function group and 16%, 29% and 38% higher geometric mean AUC_{inf} compared to subjects with normal renal function (24 hr CLcr=100 mL/min). Even at the extreme of 15 mL/min 24 hr CLcr, apixaban exposure was estimated to be 44% higher than that in subjects with normal renal function (Table 3). Further exploration of the relationship between apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$ and other methods of assessing renal function (iohexol CLT, C-G estimated CLcr and MDRD estimated CLcr) was performed. Consistent with 24 h CLcr, a similar inverse relationship was observed between apixaban AUC and each of these measures of renal function, although the results appear to be more variable when based on C-G and MDRD estimations of renal function.

Impaired Hepatic Function

A multicentre, open label, non-randomized, single dose study examined the potential effect of hepatic impairment on apixaban PK (**CV185025)**. No subjects with severe hepatic impairment (Child Pugh Class C) were studied due to the increased risk of bleeding in this population.[9] The study was powered to detect a 1.5 fold increase in geometric means of C_{max} and AUC_{inf} in hepatically impaired subjects as compared to healthy controls. There were no statistically significant differences between healthy subjects and mild or moderately hepatically impaired subjects in PK: all of the 90% CI for the impaired: healthy ratios contained 1. Despite the lack of statistical significance the upper range of the 90% CI for $AUC_{(0-t)}$ and AUC_{inf} exceeded the usual 1.25 value for strict bioequivalence but did not exceed 1.5, the *a priori* pre-determined limit for a significant clinical effect. Both mild and moderate hepatic impairment has an effect on systemic exposure to apixaban but this is unlikely to be of clinical significance. The lack of change in apixaban CLT/F observed in this study is consistent with the multiple elimination pathways identified for apixaban. Given the limited influence that impaired hepatic function had on apixaban exposure, dose adjustment for hepatic function alone is not recommended. However there are no data for severe hepatic impairment. Apixaban is contraindicated in severe hepatic impairment due to potential for an increased risk of bleeding.

Evaluator's overall comments on PK in special populations

An extensive group of studies have been undertaken to evaluate a number of pertinent factors likely to alter the PK of apixaban in special populations. While the sample size in studies of the effects of age, gender and race appear to be adequately powered to evaluate these potential factors on apixaban PK, the sample sizes for renal and hepatic impairment are relatively small by comparison. The population PK study extends the assessment of the potential effect of renal function on apixaban PK by using clearance as one of the factors in

[9] The **Child-Pugh score** is used to assess the prognosis of chronic liver disease. The score employs five clinical measures of liver disease. Each measure is scored 1-3, with 3 indicating most severe derangement.

the model. Thus the derived PK model was able to assess the potential of changes in renal function to alter apixaban PK. Nevertheless there were no studies in patients with severe renal impairment to address this issue *in vivo*. Similarly there were no studies in severe hepatic impairment which addressed the potential PK differences that may arise in such a patient population. Needless to say the effects of such potential changes on PD parameters particularly bleeding events has also not been addressed. Even though apixaban has multiple routes of metabolism it does depend on CYP enzymes for at least part of the metabolic process. Thus further studies in these two patient populations would be helpful.

Interactions

In vitro interactions

The potential of apixaban to inhibit or induce CYP was minimal. The median inhibitory concentration (IC_{50}) values for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 and CYP3A4 by apixaban were >45 μM in human liver microsomes, in excess of the mean peak plasma concentration in humans receiving the highest tested dose: 10 mg bd (0.79 μM total drug concentration) (**CV185046**). While there was weak inhibition of CYP2C19 (IC_{50} between 20 and 30 μM), there was no evidence of time or metabolism dependent inhibition of CYP3A4 activity (**DCN 930002493, 930024178**). At concentrations up to 20 μM, apixaban did not induce CYP1A2, CYP2B6 or CYP3A4 activity in human hepatocytes (**DCN 930002493**, **930024170**), making it unlikely that it will affect the metabolism of CYP substrates. Since apixaban is a substrate for the P-gp transporter (**DCN 930002493, DCN 930037717, DCN 930017758**), its absorption may be affected by P-gp inhibitors. The failure of apixaban to inhibit P-gp (**DCN 930017758**) suggests that apixaban will not affect the absorption of drugs that are P-gp substrates. This potential mechanism for drug-drug interaction was investigated by examining the effect of apixaban taken with naproxen, a common non-steroidal antiinflammatory drug (**CV185054**). The effect of naproxen on the bi-directional permeability of apixaban was examined with Caco-2 cell monolayers (**DCN 930037717**) and BCRP-transfected MDCKII cell monolayers (**DCN 930037784**). In Caco-2 cells, treatment with naproxen (6mM) led to a 42% inhibition of efflux of apixaban (3μM). Naproxen (8mM) showed little effect on the transport of apixaban (5μM) in the BCRP-transfected MDCKII cell monolayers. Based on these *in vitro* data, the 61% and 54% increase in apixaban C_{max} and AUC_{inf}, respectively, upon coadministration of naproxen (**CV185054**) is consistent with inhibition of P-gp-mediated apixaban efflux in the intestine leading to increased absorption.

In vivo interactions

Apixaban was studied in 12 drug interaction studies. The potential for PK or PD interactions was assessed for drugs which may be commonly coadministered with apixaban. Based on nonclinical data, the potential for other drugs to affect apixaban exposure appear to be primarily related to the inhibition or induction of CYP3A4 and 3A5 metabolism and/or P-gp mediated efflux and represented the greatest potential for drug interactions involving apixaban.

An open label, non-randomized, crossover study was conducted in 20 healthy subjects to examine the effect of ketoconazole on apixaban PK (**CV185026**). Coadministration of ketoconazole was associated with a 62% increase in C_{max} and a 100% increase in AUC_{inf} of apixaban. Inhibition of both CYP3A4 and P-gp would be consistent with the observed effect. The extent of increase in apixaban exposure was not as high (> fivefold) as that for compounds that are considered to be sensitive substrates for CYP3A4 (for example, midazolam, triazolam). The average twofold increase in AUC indicates that apixaban is not a sensitive substrate for CYP3A4.

The effect of diltiazem on apixaban PK was examined in an open label study in 18 healthy subjects (**CV185032)**. Following multiple daily doses of diltiazem, C_{min} values did not change appreciably beyond Day 8, indicating that steady state concentrations were achieved. A 40% increase in apixaban AUC and a 31% increase in C_{max} were observed when apixaban was coadministered with diltiazem, a moderate inhibitor of CYP3A4 and an inhibitor of P-gp based on *in vitro* data. Apixaban $t_{½}$ was similar when administered alone and in the presence of diltiazem (17 h and 16 h, respectively). Assuming that the volume of distribution of apixaban was not altered by diltiazem, this observation suggests that a change in systemic clearance was not solely responsible for the observed effect of diltiazem on apixaban exposure and that increased apixaban bioavailability contributed to the higher apixaban concentrations.

An examination of the potential interaction between apixaban and naproxen was investigated in an open label, crossover study (**CV185054).** When apixaban 10 mg was coadministered with naproxen 500 mg, the geometric means for C_{max}, AUC_{inf} and $AUC_{(0-t)}$ of apixaban increased by 61%, 54% and 55%, respectively, relative to those observed following administration of apixaban 10 mg alone. Apixaban T_{max} and $t_{½}$ remained unchanged. Naproxen is a P-gp inhibitor at concentrations that occur in the GIT following administration of ≥ 500 mg naproxen. Thus, the effect of naproxen on apixaban exposure was attributed to the pre-systemic inhibition of P-gp mediated efflux of apixaban, resulting in higher apixaban bioavailability.

The potential interaction between rifampin and apixaban was studied in an open label trial in 20 healthy subjects (**CV185045)**. Rifampin decreased apixaban exposure for both PO and IV doses. For PO doses, rifampin reduced apixaban C_{max} by 42%, $AUC_{(0-t)}$ by 53%, and AUC_{inf} by 54%. For IV doses, rifampin reduced apixaban $AUC_{(0-t)}$ and AUC_{inf} by 39%. Apixaban C_{max} after IV administration was only slightly reduced (13%) by rifampin. Dose adjusted apixaban F was 49% for apixaban alone and 37% for apixaban in the presence of rifampin, a reduction of approximately 25%. Apixaban CLT increased by ~1.6 fold upon coadministration of IV apixaban and rifampin while renal clearance and Vss did not change. In the absence of rifampin, CLR (0.97 L/h) accounted for approximately 34% of CLT (2.82 L/h) after IV administration of apixaban. After PO coadministration of apixaban and rifampin, apixaban CLT/F doubled while CLR remained relatively consistent. The decreases in apixaban exposure in the presence of rifampin can be attributed to the increase in non-renal clearance. The findings of this study suggest that inducers of CYP enzymes and P-gp will likely reduce the apixaban exposure.

An open label study in 23 healthy subjects evaluated the potential interaction between apixaban and digoxin (**CV185028)**. The 90% CIs for the ratios of geometric means of digoxin C_{max} and AUCτ with and without apixaban were within the equivalence interval indicating an absence of interaction. At steady state the mean trough concentrations for apixaban on Days 18, 19, and 20 were 49.13 ± 25.66 ng/mL, 49.60 ± 23.27 ng/mL, and 48.99 ± 19.48 ng/mL, respectively, suggesting that apixaban had reached steady state by Day 20. The findings of this study also suggest that there is a low potential for apixaban to affect the PK of other P-gp substrates since digoxin is a commonly used P-gp probe substrate.

Safety and tolerability of apixaban administration with aspirin was assessed in a double blind, placebo controlled, randomized, parallel group study in 17 healthy subjects (**CV185002B)**. Apixaban had no effect on acetylsalicylic acid (ASA) AUCτ or C_{max} based on comparisons of exposure before and after apixaban coadministration. Although ASA C_{max} was 26% higher after administration with apixaban, a similar increase was seen in placebo treated subjects over the same time period. There was no evident PK interaction.

The safety and tolerability of apixaban administered with clopidogrel was determined in a study in healthy volunteers (**CV185005)**. Apixaban steady state PK parameters were in agreement with previous studies suggesting that clopidogrel had no evident effect on apixaban PK. Accumulation index values for apixaban were 1.30 to 1.87 in the qd and bd panels, respectively, indicating modest accumulation of apixaban to steady state. Overall, coadministration of clopidogrel 75 mg qd with apixaban 5 mg bd or 10 mg qd was generally well tolerated. There was no evident PK or PD interaction based on the limited assessment in this study.

The combination of clopidogrel and aspirin when administered with apixaban was evaluated in study (**CV185015)**. This was a randomized, double blind, placebo controlled, two treatment, parallel group study in 30 healthy volunteers. The AUCτ and C_{max} values of the clopidogrel carboxylic acid metabolite (SR26334) in this study were within the range reported in the literature. Minimal decreases in SR26334 C_{max} and AUC were seen when aspirin and apixaban were coadministered with clopidogrel. This suggests that apixaban is unlikely to have a clinically relevant effect on the PK of clopidogrel or its active metabolite. Apixaban 20 mg had little effect on aspirin PK, decreasing the C_{max} and AUCτ of the aspirin metabolite, SA, by less than 10%. The minimal decreases in SA AUC and C_{max} suggest that apixaban is unlikely to have a clinically relevant effect on the PK of aspirin. These data reinforce the results for the aspirin interaction study (**CV185002B**) and the clopidogrel interaction study (**CV185005**).

The effect of enoxaparin on apixaban PK was examined in an open label, four treatment, single dose crossover study in 20 healthy subjects (**CV185055**). Coadministration of enoxaparin with apixaban had no effect on apixaban exposure. All the 90% CIs were entirely contained within the pre-specified equivalence criterion, 80% to 125%. When 5 mg apixaban was administered 6 h before enoxaparin 40 mg, apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$ were 14%, 12% and 12% higher, respectively, relative to those observed following administration of apixaban alone. For AUC_{inf} and $AUC_{(0-t)}$, the 90% CIs were entirely contained within the pre-specified equivalence criterion, 80% to 125%. For C_{max}, the 90% CI extended slightly above the upper boundary of 125%.

Atenolol is a commonly prescribed antihypertensive agent which may be prescribed to patients requiring treatment with apixaban. The potential PK interaction was examined in an open label, three period, three treatment, crossover study in 15 healthy subjects (**CV185033**). Atenolol had no effect on the PK of apixaban: the 90% CI for geometric mean C_{max} and AUC_{inf} were contained within the pre-specified 70-143% equivalence interval. This broader no effect interval was chosen based on the Phase II population PK and exposure response analysis that suggested modest differences in apixaban exposure would not have a relevant impact on clinical outcome. Apixaban had no effect on atenolol C_{max} and AUC_{inf}. The 90% CI for ratios of atenolol geometric mean C_{max} and AUC_{inf} were contained within the equivalence interval of 80-125%.

The effect of famotidine, a H_2 antihistamine gastric pH suppressant and strong organic cation transporter (OCT) inhibitor on the PK of apixaban was evaluated in an open label, crossover study in 18 healthy subjects (**CV185060**). Famotidine had no effect on apixaban C_{max}, AUC_{inf} and $AUC_{(0-t)}$. The 90% CI for the ratios of geometric means for C_{max}, AUC_{inf} and $AUC_{(0-t)}$ of apixaban, with and without famotidine, were entirely contained within the equivalence interval of 80% to 125%. These data indicate that apixaban PK are not likely to be altered by alterations in gastric pH or co-administration with OCT inhibitors.

Evaluator's overall comments on PK interactions

Ketoconazole (a strong inhibitor of CYP3A4 and P-gp) had the largest effect on apixaban PK (approximately twofold increase in exposure). Care should be taken when

administering apixaban with strong CYP3A4 inhibitors*. Diltiazem, a less potent CYP3A4 and P-gp inhibitor also resulted in a 40% increase in apixaban exposure. Naproxen, an inhibitor of P-gp, resulted in an approximately 60% increase in apixaban exposure. Naproxen appeared to affect apixaban bioavailability via inhibition of P-gp mediated transport. Rifampin (a strong CYP inducer and P-gp inducer) reduced apixaban exposure by ~40% after IV administration and ~ 50% after PO administration; bioavailability was reduced 25% by rifampin. In light of the decrease in exposure following induction, care should be taken when administering apixaban with strong inducers of CYP enzymes or P-gp. Apixaban appears to have little potential to affect the PK of other P-gp substrates based on the lack of effect on digoxin exposure, a commonly used P-gp substrate. In addition, *in vitro* data indicate that apixaban is not likely to alter the metabolism of other drugs. Therefore, the potential for apixaban to affect the PK of concomitantly administered medications is low.

* Apixaban is contraindicated in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp.

Exposure relevant for safety evaluation

The effect of a supra-therapeutic apixaban dose (50 mg once daily) on the QT / QTc interval, a measure of cardiac repolarisation, was investigated in 40 healthy volunteers (**CV185031)**. Moxifloxacin, the positive control, demonstrated a characteristic prolongation of the QT interval with the Fridericia correction (QTcF) interval, confirming assay sensitivity. The QTcF increases for moxifloxacin were greater than those for placebo from Hours 1 to 24 on Day 3. The maximal placebo adjusted change from time matched baseline in the QTc interval (ΔΔQTcF) for moxifloxacin was at 3 h postdose (10.84 msec) and the pattern of QTc prolongation followed the known plasma time course of moxifloxacin. For the apixaban, ΔΔQTcF indicated that multiple dosing with a supra-therapeutic dose of apixaban had no clinically meaningful effect on QTc interval. For apixaban 10 mg and 50 mg doses, the maximal increase in ΔΔQTc occurred at 24 h postdose (1.48 and 2.11 msec, respectively). The upper bound of the 95% CI for the placebo adjusted differences for both apixaban doses were < 10 msec, indicating that apixaban had no significant effect on the QTcF interval. Secondary regression analysis provided no evidence of a positive relationship between apixaban plasma concentration and the change from time matched baseline in QTc interval (ΔQTcF). Categorical analysis showed that no subject had a QTcF interval > 450 msec or a ΔQTcF > 60 msec. PR and QRS intervals were not affected by apixaban. Apixaban had no effect on the QTc interval at concentrations exceeding those anticipated in patients who receive apixaban for VTE following TKR or THR.

Evaluator's overall conclusions on pharmacokinetics.

The main findings for apixaban PK following single or multiple PO doses in healthy subjects are that the drug exhibits linear PK over the oral dose range 2.5 mg to 10 mg bd which is well beyond that proposed for therapeutic use (2.5 mg bd) in VTE following elective total knee or hip replacement surgery. Oral bioavailability of apixaban is ~50% while the drug is highly protein bound (~87%). Maximum plasma concentrations were reached within 3 to 4 h after PO dosing. Absorption appeared to primarily occur in the small intestine. Intake with food did not affect apixaban AUC or C_{max} at the 10 mg dose. While apixaban is metabolised by CYP3A4/5, none of the metabolites appear to be pharmacologically active. The main inactive metabolite, BMS-730823 (M1, O-desmethyl apixaban sulfate), is present at approximately 25% of parent drug concentrations. Apixaban is not extensively distributed to tissues (Vss of ~21L is somewhat less than that of total body water). Following intravenous administration, the total body clearance (CLT) of apixaban is low, ~55 mL/min (3.3 L/h), with renal clearance accounting for ~ 27% of

CLT. Apixaban reaches steady state concentrations after 3 days of dosing, consistent with the $t_{½}$ of approximately 12 hours and twice daily dosing. The effects of extrinsic and intrinsic factors on apixaban PK were well characterized. Generally apixaban does not require dose modification for the following factors: age, gender, body weight (<30% change in PK), race, mild to severe renal impairment* (<50% increase in apixaban exposure), mild to moderate hepatic impairment, coadministration of strong inhibitors of both CYP3A4 and P-gp* (~twofold increase apixaban exposure after ketoconazole), coadministration of strong inducers of either CYP3A4 or P-gp (~50% decrease in apixaban exposure after rifampin). There is a low potential for apixaban to affect the PK of concomitantly administered medications. Apixaban daily doses up to 50 mg were not associated with prolongation of the QTc interval. The effects of smoking, diet composition, herbal products and alcohol use on the PK of apixaban have not been studied.

* Apixaban is contraindicated in patients with severe renal impairment with a creatinine clearance < 15 mL/min and in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp.

Pharmacodynamics

Introduction

Apixaban PD studies evaluated concentration-response relationships with clotting time assays: international normalised ration (INR), prothrombin time (PT), activated partial thromboplastin time (aPTT) and modified PT (mPT), as well as anti-Xa activity, given that these assessments are relevant to the direct reversible effect of apixaban on coagulation Xa (FXa). In addition, measures such as *ex vivo* thrombin generation, template bleeding time and agonist induced (adenosine 5'-diphosphate, arachidonic acid, or collagen) platelet aggregation were explored in a limited number of studies.

Mechanism of action

Apixaban is an orally active, selective inhibitor of FXa that reversibly binds directly to the active site of FXa, and exerts anticoagulant and antithrombotic effects by diminishing the conversion of prothrombin to thrombin. As the common mediator of both extrinsic and intrinsic activation of coagulation, FXa is the sole physiological mediator of thrombin formation. Thrombin, through its actions on fibrin formation and platelet activation, is a key mediator of thrombosis in both the venous and arterial circulation. Inhibition of thrombin generation produces antithrombotic effects. Apixaban has been developed for the prevention and treatment of thrombotic diseases and the present application focuses on prevention of VTE in patients undergoing THR or TKR.

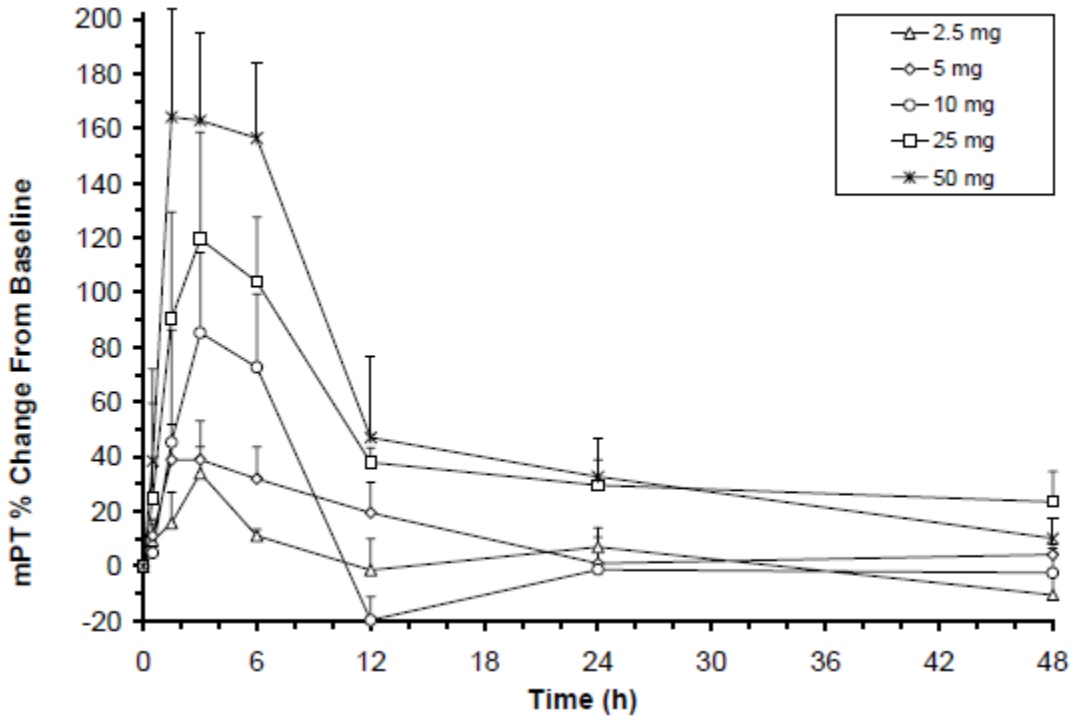
Primary pharmacology

Effect on Clotting Time Assessments (aPTT, INR, mPT)

Clotting time assessments were integrated across the clinical pharmacology program to assess the relationship to apixaban plasma concentration. The effect of apixaban on clotting time tests, INR, PT and aPTT, as well as mPT have been evaluated following single dose (**CV185001, CV185013, CV185054, CV185055, CV185022, CV185018, CV185025, CV1850059, CV185008**) and multiple dose administration (**CV185002A, CV185046, CV185002B, CV185005**). These studies covered a dose range from 0.5 to 50 mg. This experience included patients following TKR (**CV185010**). Dose related increases in INR and aPTT were observed following administration of apixaban single PO doses of 2.5 to 50 mg to healthy subjects. INR appeared to have more pronounced changes in the presence of apixaban than aPTT. A linear model appeared to be suitable for describing the relationship between INR and apixaban plasma concentration, while a maximum effect (E_{max}) model best described the relationship for aPTT. While the relationship was variable

for both clotting tests, clotting time prolongation closely followed the apixaban concentration time profile, where the maximal clotting time occurred near the apixaban T_{max} and returned to baseline coincident with the apixaban elimination phase (Figure 2). Similar observations were made in special populations, such as subjects with hepatic impairment, renal impairment, advanced age, as well as the intended patient population. The mPT assay was developed to improve the dynamic range of the PT assay for better measurement of the effect of apixaban. As expected, the magnitude of change in mPT was significantly greater than that for PT/INR for a given apixaban concentration range. Similar to PT/INR, mPT also showed dose related increases in clotting time with strong concordance with apixaban plasma concentration. Different than PT/INR and aPTT, mPT appeared to have a more curvilinear relationship with apixaban plasma concentration. Based on an assessment of the clinical application of the mPT assay, it was concluded that it was not suitable as a PD measure.

Figure 2: %mPT change from baseline versus time



Effect on anti-Xa Activity

Anti-Xa activity was evaluated following single dose **CV185020, CV185058, CV185054, CV185055, CV185022, CV185018, CV185025, CV1850059)** and multiple dose (**CV185046**, **CV185058**) administration across the dose range 2.5 to 20 mg. This experience included patients following THR or TKR surgery (**CV185047, CV185035**). Concentration related increases in anti-Xa activity were observed following administration of apixaban. A linear model best described the relationship between anti-Xa activity and apixaban plasma concentration. Since anti-Xa activity and apixaban plasma concentration were highly correlated, changes in anti-Xa activity closely reflect that of the apixaban concentration time profile reaching maximal values near the apixaban T_{max} and returning to baseline coincident with apixaban elimination. In healthy subjects, mean peak anti-Xa activity was approximately 1.3 IU/mL and 5.5 IU/mL at apixaban steady state following multiple doses of 2.5 mg bd and 10 mg bd, respectively. Mean peak and trough anti-Xa values were approximately 1.4 IU/mL and 0.75 IU/mL, respectively, in patients

who received apixaban 2.5 mg bd for VTE following TKR or THR surgery (**CV185047, CV185035**). When evaluated in specific populations such as hepatic impairment, renal impairment and the elderly, anti-Xa activity directly reflected the observed apixaban plasma concentration within that population. Thus the underlying disorder had no effect on the relationship between apixaban plasma concentration and anti-Xa activity.

Effect on Thrombin Generation

Ex-vivo thrombin generation mediated by tissue factor in platelet poor plasma has been measured in healthy subjects (**CV185013**). Single doses of apixaban produced transient, dose related changes in parameters of the thrombin generation curve. Changes included an increase in the lag time and time to peak and a decrease in the peak value (maximum thrombin concentration) and endogenous thrombin potential (ETP). Lag time and time to peak increased by approximately 65% three hours after administration of 2.5 mg apixaban. Peak values and ETP decreased by approximately 40% and 12.5%, respectively, following administration of 2.5 mg apixaban. The effect of apixaban on thrombin generation parameters was evident for ≥12 h after dosing, demonstrating that apixaban PD activity would be evident over a 12 h dosing interval. The observed changes in thrombin generation parameters represent the expected effects of a direct factor Xa inhibitor in prolonging the initiation phase and inhibiting the propagation phase of thrombin generation.

Effect on Platelet Aggregation

Apixaban has no direct effect on platelet aggregation. Apixaban indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents the conversion of prothrombin to thrombin, reducing the amount of thrombin available to stimulate platelet aggregation. The effect of apixaban on platelet aggregation has been assessed in several studies in the presence (**CV185054, CV185002B, CV185005, CV185015**) or absence (**CV185054**) of platelet aggregation inhibitors, aspirin, clopidogrel, and naproxen. Changes in platelet aggregation seen in these studies were attributed to the known effects of the respective anti-platelet agents studied. Apixaban alone had no effect on arachidonic acid induced platelet aggregation (**CV185054**).

Effect on Bleeding Time

The effect of apixaban on template bleeding time has been evaluated after single or multiple dose administration of apixaban over the dose range 0.5 mg to 50 mg. This included subjects who also received concomitant anti-platelet agents **(CV185001 CV185002A CV185002B CV185005 CV185015 CV185054 CV185013).** Within individual studies, there was no effect of apixaban alone on bleeding time. Similarly, in the presence of anti-platelet agents, the observed effect on bleeding time was attributed to the known effects of the anti-platelet agent. Analysis of data pooled across studies, where bleeding time was determined following administration of apixaban alone, suggests a trend for a weak direct relationship with increasing apixaban plasma concentration. This observation is not considered to be clinically relevant given that the results are highly variable, and few values exceed the reference range of the assays, even following administration of apixaban 50 mg, a dose 10 times higher than the proposed clinical dose of 2.5 mg bd.

Secondary pharmacology

Apixaban is selective for FXa; pharmacological effects are directly related to its primary mechanism of action. Secondary pharmacological effects have not been observed.

Population Exposure Response Analysis

An exposure response (ER) analysis was performed to relate apixaban exposure to efficacy and safety endpoints. Efficacy events were defined as the composite of symptomatic and asymptomatic deep vein thrombosis, pulmonary embolism, and all cause death. The ER model for clinical efficacy showed a relatively flat ER relationship for daily doses ranging from 5 mg to 20 mg and predicted a trend for improved efficacy for the bd versus once daily dosing regimen in TKR surgery subjects. The safety endpoint used in this analysis was the frequency of bleeding, defined as any bleeding (AB), which included the following: major bleeding (MJB), minor bleeding (MNB), clinically relevant non-major bleed (CRNMB) and potentially significant non-overt bleed (PSNB). The ER model for clinical safety predicted that the risk of AB for 2.5 mg bd apixaban to be 6.2% and 9.5% for TKR and THR surgery, respectively, which are similar to the bleeding rates associated with enoxaparin 40 mg qd (6.82% in TKR and 11.0% in THR). The ER analysis was also utilized to guide dosing recommendations for selected intrinsic and extrinsic factors that affect apixaban exposure (that is, severe renal impairment and strong inhibitors of CYP3A4 and P-gp). The ER model predicts that the risk of AB in subjects with severe renal impairment would be expected to increase from 6.2% to 6.8% and from 9.5% to 10% in TKR and THR surgery, respectively. The ER model for clinical safety predicts the risk of AB for a twofold (100%) increase in apixaban exposure (that is, that observed following coadministration of apixaban with ketoconazole) to be 7.2% and 11% in TKR and THR surgery, respectively; while a threefold (200%) increase in exposure is predicted to result in AB risks of 8.5% and 13% in TKR and THR surgery, respectively. The increases in apixaban exposure anticipated for these intrinsic and extrinsic factors are unlikely to be clinically relevant based on the increase in the probability of bleeding predicted by ER modelling. The model suggests that apixaban does not require dose adjustment or contraindication when administered in subjects with severe renal impairment (CLcr: 15-30 mL/min). There is limited clinical experience with subjects taking either CYP3A4 or P-gp inhibitors. Administration of these agents with apixaban is contraindicated. In the case of strong inducers of both CYP3A4 and P-gp, Phase II ER analysis for VTE events indicated a flat relationship over the dose range evaluated (2.5 mg bd to 10 mg bd, 5 mg qd to 20 mg qd).

Pharmacodynamic interactions with other medicinal products or substances

An open label single dose study in 21 healthy subjects evaluated the effect of apixaban (10 mg), naproxen (500 mg) and the combination on PD parameters (**CV185054**). Changes in INR and anti-Xa activity observed in this study corresponded to the increase in apixaban plasma concentration. Apixaban did not have a clinically relevant effect on bleeding time. In addition, the changes in arachidonic acid induced platelet aggregation were consistent with the known effect of naproxen; apixaban did not appear to have an effect on this measure.

The effect of apixaban administration with aspirin on PD measures was conducted as a double blind, placebo controlled randomized, parallel group study in 17 volunteers (**CV185002B**). INR, mPT and aPTT were unaffected by aspirin treatment; all increased in subjects concomitantly treated with aspirin + apixaban. The relative increase in mPT (% increase from baseline) was more pronounced than that for INR or aPTT [mPT (56%) >INR (18%) >aPTT (12%)]. The time profile and magnitude of increases in INR, mPT and aPTT in subjects treated with aspirin + apixaban were consistent with the expected effect of apixaban. Treatment with aspirin 325 mg qd for 5 days almost completely inhibited arachidonic acid induced platelet aggregation, an expected PD response. Following 7 days of coadministration of apixaban 5 mg bd with aspirin, there was no diminution in the effect of aspirin on platelet aggregation (5.5% and 4.0% in subjects administered aspirin, with or without apixaban, respectively). Similarly, increases in bleeding time were

consistent with known effects of aspirin. The addition of apixaban 5 mg bd to aspirin did not result in any evident additional increase in bleeding time.

Apixaban was administered with clopidogrel in a double blind, placebo controlled study in healthy subjects (**CV185005**). Treatment with clopidogrel substantially inhibited ADP induced platelet aggregation (mean aggregation decreased 50% to 62% from baseline at 4 h), slightly inhibited arachidonic acid induced platelet aggregation (<20% mean decrease from baseline) and did not inhibit collagen induced platelet aggregation (<2% mean change from baseline) in all treatment groups. Coadministration of clopidogrel + apixaban for 5 days was not associated with an obvious additive or inhibitory effect on agonist induced platelet aggregation compared to clopidogrel alone. Similarly, increases in bleeding time were attributed to the effect of clopidogrel. There were no evident differences in mean bleeding time between subjects receiving clopidogrel with placebo, apixaban 5 mg bd or apixaban 10 mg qd.

The combination of apixaban, clopidogrel and aspirin was assessed in a randomized, double blind, placebo controlled study in 30 healthy subjects (**CV185015**). Concomitant treatment with apixaban 20 mg did not alter the effect of clopidogrel + aspirin on either ADP or arachidonic acid induced platelet aggregation. ADP induced platelet aggregation decreased from baseline comparably (~50% decrease) in apixaban and placebo treated subjects; these effects were similar to the effect of clopidogrel observed in Study **CV185005**. Similarly, arachidonic acid induced platelet aggregation decreased change from baseline (~70% decrease) was comparable in subjects treated with apixaban and placebo treated subjects; these effects were similar to that observed for aspirin in Study **CV185002B**. These PD data further support the assessment that the 10% decrease in clopidogrel and aspirin metabolite (SR26334, SA respectively) exposures is not likely to have any clinically relevant impact on the effectiveness of these agents.

The potential for interaction between apixaban and enoxaparin was evaluated in an open label four sequence single dose crossover study in 20 healthy subjects (**CV185055**). Mean baseline INR values ranged from 0.92 to 0.93 for all treatment groups. Little change in INR was observed for any treatment. The maximum INR values ranged from 0.98 to 1.04 across treatments. Following administration of enoxaparin alone, anti-Xa activity was below the limit of quantitation at the 17 and 24 h time points. Administration of apixaban 5 mg alone resulted in a higher peak anti-Xa activity than that observed following administration of enoxaparin 40 mg alone (1.36 versus 0.42 U/mL, respectively). As expected, coadministration of apixaban and enoxaparin resulted in higher anti-Xa activity, when expressed as anti-Xa C_{max} (42%) and as anti-Xa $AUC_{(0\text{-}T)}$ (52%), compared to that following administration of either agent alone. Anti-Xa C_{max} and $AUC_{(0\text{-}t)}$ were 15% and 58% higher, respectively, following administration of enoxaparin 6 h after apixaban, relative to values observed following administration of apixaban alone. Overall, these data are consistent with the expected additive effect on factor Xa following coadministration of 2 reversible factor Xa inhibitors.

Evaluator's overall conclusions on pharmacodynamics

Apixaban is a potent, direct, reversible inhibitor of coagulation factor Xa. Anti-FXa activity exhibits a close, direct, linear relationship with apixaban plasma concentration. Steady state peak and trough anti-FXa activity with apixaban 2.5 mg bd dosing are expected to be 1.3 IU/mL (5th /95th percentile 0.67-2.4 IU/mL) and 0.84 IU/mL (5th /95th percentile 0.37-1.8 IU/mL), respectively, in subjects that receive apixaban for VTE following TKR or THR surgery. Apixaban prolongs clotting time measurements such as INR, prothrombin time, and activated partial thromboplastin time. Following administration of 2.5 mg bd, changes in clotting time measurements are small and variable. The anti-FXa assay may be useful for monitoring in situations where knowledge of apixaban exposure may help to

inform clinical decisions. Apixaban does not exhibit any secondary or off target pharmacologic effects, including an effect on the QTc interval.

Efficacy

Introduction

Trial subjects in the key clinical efficacy studies underwent either THR or TKR, both of which are associated with a high risk of VTE. The American College of Chest Physicians (ACCP) guidelines for prevention of VTE state that distal DVT, proximal DVT, clinically apparent PE and fatal PE occur in 40-80%, 10-20%, 4-10% and 0.2-5% of patients respectively.[10] Prophylactic antithrombotic therapy has proved highly effective in lower limb surgery but it is limited by a significant risk of bleeding.

The overall risk of VTE is substantial in TKR and THR but the risk is time dependent. Risk for DVT following TKR is maximal between 1-2 weeks while DVT risk following THR is greatest at approximately 30 days after surgery. Treatment guidelines recommend longer treatment for THR than TKR and this was reflected in the design of the studies presented.

Enoxaparin is the most widely studied low molecular weight heparin (LMWH) and it has replaced heparin and warfarin as the gold standard for VTE prophylaxis. However, it must be given SC and it causes injection site reactions; it is usually given before surgery and there is a small risk of clinically significant thrombocytopenia.

To support this application, four key studies were conducted. They were all robustly designed, international, multicentre, randomized, double blind, double dummy and active controlled. The study designs reflected the consensus opinion of clinical, health authority and regulatory guidelines for VTE prophylaxis. They all complied with full ICH Good Clinical Practice guidelines, were adequately monitored and selected sites were subjected to internal company audit.

All venograms and suspected VTE events (DVT and PE), including diagnostic test results, were reviewed and adjudicated by the same independent central adjudication committee (ICAC) who were blinded to treatment and study results throughout the study period. They also reviewed and adjudicated all bleeding, arterial thrombotic events, thrombocytopenia and deaths.

The primary efficacy and safety endpoints were similar in all studies. However, many of the data from the individual studies cannot be pooled because of different enoxaparin comparator doses and the different duration of treatment for the two indications. Nonetheless it is appropriate to pool data from studies CV185010 and CV185034 in TKR because the indication and the dose of enoxaparin were the same (30 mg q12h). Despite the different indications and treatment durations for TKR and THR, it is also appropriate to combine certain data sets in CV185047 and CV 185035 because the enoxaparin comparator dose was the same (40 mg qd).

A dosing regimen for the Phase III studies was evaluated based on data from CV185010, a dose ranging Phase II study comparing apixaban with warfarin titrated to INR and enoxaparin 30 mg q12h, the approved dose in the US for TKR. Dose response trends were identified and apixaban 2.5 mg bd was selected as a regimen which offered similar or improved efficacy, with no increase in bleeding events when compared with enoxaparin.

[10] Geerts WH, Bergqvist D, Pineo GF et al. Prevention of thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th Ed). Chest 2008; 133: 381-453S.

The primary endpoint in all studies was the composite endpoint of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and all cause death during the Intended Treatment Period. For the pivotal studies CV185047 (TKR) and CV185035 (THR), the key secondary endpoint was major VTE (adjudicated proximal DVT, non-fatal PE, and VTE related death) during the Intended Treatment Period. Subjects were assessed for signs and symptoms suggestive of VTE and those considered positive were referred for appropriate objective imaging investigation. All VTE and death events were adjudicated by the ICAC. As mandated by both the Committee for Medicinal Products for Human Use of the EU and FDA, the gold standard for asymptomatic DVT is bilateral ascending venography and the objective was to achieve a ≤ 30% composite rate of ' not done' or 'non-evaluable' venograms. Every attempt was made in the protocol designs to pursue these and other endpoints critical to the analyses.

The validity and relevance of the primary efficacy endpoint for VTEp has been re-assessed since these studies were commenced. The clinical significance of peripheral DVT, as an independent endpoint or part of a composite event, has been downgraded. The primary composite endpoint preferred by the CHMP since 2008 is the more clinically significant criterion of major VTE (proximal DVT, non-fatal PE and VTE related death). Both endpoints were assessed and compared in the studies presented.

The Phase III studies shared predefined statistical criteria for non-inferiority (NI) and superiority. For NI, the upper bound of the 95% CI for RR was set at 1.25. This difference is clinically meaningful and it is generally agreed to be appropriate by authorities and used in similar published VTEp trials. The sample size was based on event rates for the primary composite efficacy endpoint from the dose ranging study CV185010 (9.9% for apixaban 2.5 mg bd versus 15.6% for enoxaparin 30 mg q12h). These outcome rates were also similar to comparable published VTEp studies.

Predefined subgroup analyses were performed on data for subgroups of clinical interest, including race, age, gender, BMI and renal impairment. To increase the sensitivity of the analyses, some data were pooled from the two Phase III studies with a common comparator (CV185035 and CV185047) and all other Phase II and III studies.

Dose response study

CV185010

This was a Phase II randomized, double blind (apixaban and enoxaparin), active controlled (enoxaparin and warfarin), parallel arm, dose response study of the oral Factor Xa inhibitor apixaban in subjects undergoing elective total knee replacement surgery.

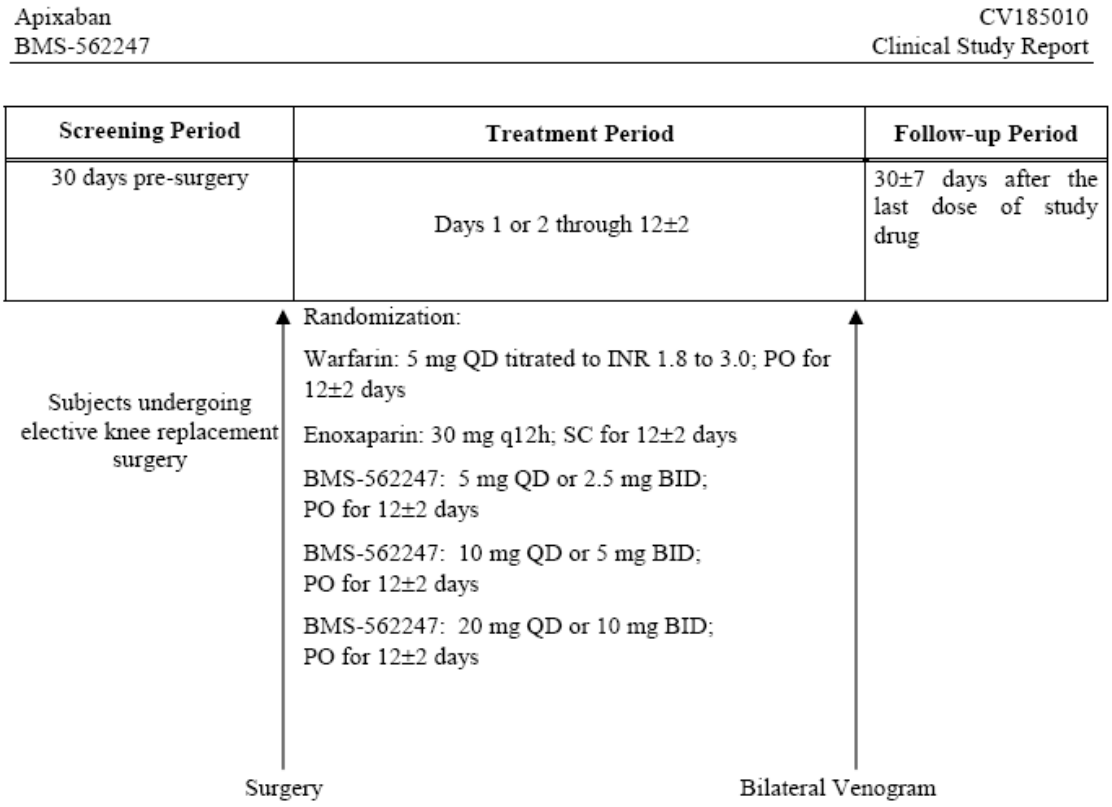
Methods

A total of 100 centres in 8 countries recruited 1217 patients who were randomised into one of eight treatment groups of approximately 150 patients. Subjects were randomised on the day of surgery to receive one of the following:

- Oral warfarin titrated to INR 1.8-3.0
- SC enoxaparin 30 mg q12h or
- One of six doses of oral apixaban (5, 10 or 20 mg qd or 2.5, 5 or 10 mg bd)

The warfarin treatment arm was open label. The apixaban and enoxaparin study medications were double dummy, blinded using placebo to match the comparator doses. Enoxaparin and apixaban were started 12-24 hours after wound closure for 12 +/-2 days. Subjects were followed up to Day 42 +/- 7 (an average of 30 days after the last dose of study medication). The treatment scheme is shown in Figure 3.

Figure 3: Treatment scheme for CV185010



Subjects were instructed on the correct administration of study medication and asked to complete a daily dosing diary to document study compliance. While hospitalised, subjects were evaluated daily for symptomatic VTE and bleeding, and a mandatory bilateral ascending contrast venogram was performed at the end of treatment.

After discharge, subjects were required to report all adverse events (AEs) and any symptoms of DVT, PE or bleeding. Subjects with symptoms of VTE returned to the hospital for appropriate diagnostic investigations, which could include ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET) or other nuclear scans. The evaluation period for the primary endpoints started with the first dose and continued until two days after the last dose of randomized treatment.

Objectives

The primary objective was to detect a dose response relationship amongst three apixaban bd dose groups (2.5, 5 and 10 mg) and three apixaban qd dose groups (5, 10 and 20 mg).

Secondary objectives were to assess the effects of qd and bd dosing on the primary endpoint; to assess the effects of qd and bd dosing on major and minor bleeding; and to characterize the PK profile of apixaban.

Tertiary objectives were to characterize the PD profile of apixaban; to explore the relationship between PK/PD/efficacy and safety for apixaban; and to assess the effects of apixaban, enoxaparin and warfarin on a range of single efficacy and safety endpoints.

Study participants

Key inclusion criteria were: subjects undergoing elective unilateral total knee replacement; and subjects who were willing and able to undergo bilateral ascending venography.

Key exclusion criteria were: bleeding or pro-thrombotic disorders; recent GI bleeding, significant haemorrhage or haematuria; known VTE within previous 12 months; recent stroke, myocardial infarction or heart failure; creatinine clearance <30mL/min; ALT, AST or bilirubin >1.5x the upper limit of normal (ULN); and treatment with medications affecting coagulation or platelet function.

Prohibited medications included dextrans, fibrinolytics and anti-platelet agents. Cyclooxygenase (Cox)-2 selective non-steroidal antiinflammatory drugs (NSAIDs) were permitted but discouraged. All prohibited therapies could be started in the follow up period at investigator discretion.

Study therapy was immediately withdrawn for reasons including withdrawal of consent; signs or symptoms suggestive of lower limb DVT, confirmed by ultrasound or venography; signs or symptoms of PE, confirmed by investigations such as V/Q scan or angiography; significant AE and death.

Outcomes / endpoints

The primary efficacy endpoint was the composite endpoint of asymptomatic and symptomatic DVT, non-fatal PE and all cause death (VTE/all cause death) during the evaluation period as confirmed by the blinded adjudicating panel (ICAC).

The main secondary efficacy endpoint was the composite of adjudicated proximal DVT, non-fatal PE, and all cause death during the evaluation period.

Statistical considerations

With the exception of the warfarin arm, subjects and investigators were blind to the randomized treatment. All VTE and bleeding endpoints were assessed and adjudicated by the ICAC who were also blind to the randomized treatment and to study results.

With 150 subjects in each group there was 82% power to detect a dose response if the true rates for the primary endpoint were 16%, 8% and 4% respectively.

Approximately 150 subjects were treated in each group and approximately 90% of each group completed treatment. Although withdrawals due to adverse events were comparable, discontinuations due to AEs was slightly higher with the proposed apixaban 2.5 mg bd (5.9%) compared with enoxaparin (2.6%).

Treatment was interrupted in 22 subjects treated with warfarin, 3 subjects treated with apixaban and no subject treated with enoxaparin. All subjects were >80% compliant with treatment with the exception of 5 subjects treated with apixaban and 20 subjects treated with warfarin.

Approximately 98% of randomized subjects received at least one dose of the study drug and 92% subjects were treated for 7-14 days. The mean exposure was approximately 10.5 days in each group. The time from surgery to first dose was also comparable, approximately 20 hours in each group.

The groups were evenly balanced for characteristics including age, gender, race and geographical region. Most subjects were male (50-60%), average age was ~66 years and nearly all were White.

Approximately 90% of subjects in each arm completed the double blind treatment period. Approximately 60-70% of subjects were evaluable for the primary endpoint analysis.

Events during the Evaluation period

The incidence of VTE and all cause death during the evaluation period was 15.6% in the enoxaparin group, 26.6% in the warfarin group, and ranged from 5.5% - 12.4% in the apixaban groups (Table 4).

Table 4: Comparison of incidences of VTE/all cause death

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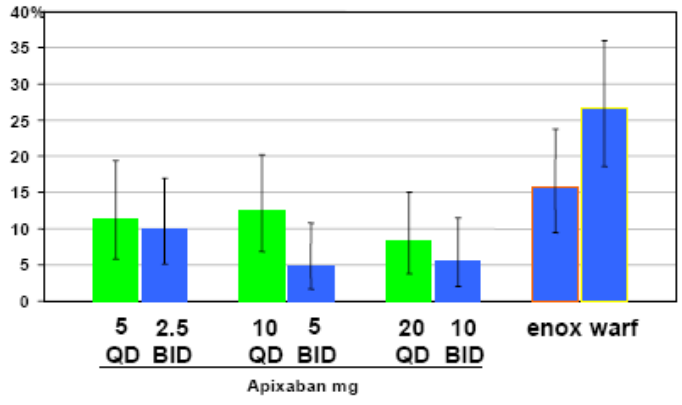
Comparison of Incidences of VTE/All-cause Death during the Evaluation Period

	BMS QD 5mg (N= 97)	BMS QD 10mg (N= 105)	BMS QD 20mg (N= 110)	BMS BID 2.5mg (N= 111)	BMS BID 5mg (N= 105)	BMS BID 10mg (N= 110)	Enoxaparin (N = 109)	Warfarin (N = 109)
VTE / All-cause Death, n	11	13	9	11	5	6	17	29
Event rate (%)	11.3	12.4	8.2	9.9	4.8	5.5	15.6	26.6
95% CI	(5.8, 19.4)	(6.8, 20.2)	(3.8, 15.0)	(5.1, 17.0)	(1.6, 10.8)	(2.0, 11.5)	(9.4, 23.8)	(18.6, 35.9)
Individual Components								
DVT, n	11	13	8	10	5	5	15	29
Symptomatic PE, n	0	0	1	0	0	1	2	0
Death, n	0	0	0	1	0	0	0	0
Comparisons to BMS Low Dose								
Diff (%) (High - Low)	N/A	1.0	-3.2	N/A	-5.1	-4.5	N/A	N/A
95% CI		(-8.3, 10.4)	(-12.0, 5.3)		(-12.8, 2.0)	(-12.2, 2.9)		
Comparisons to Enoxaparin								
Ratio (%) (BMS/Enox)	0.73	0.79	0.52	0.64	0.31	0.35	N/A	N/A
95% CI	(0.33, 1.49)	(0.38, 1.56)	(0.23, 1.11)	(0.29, 1.31)	(0.09, 0.77)	(0.11, 0.82)		
Diff (%) (BMS-Enox)	-4.3	-3.2	-7.4	-5.7	-10.8	-10.1		
95% CI	(-14.0, 5.4)	(-13.0, 6.4)	(-16.5, 1.3)	(-14.9, 3.3)	(-19.5, -2.7)	(-18.9, -1.9)		
Comparisons to Warfarin								
Ratio (%) (BMS/Warf)	0.43	0.47	0.31	0.37	0.18	0.21	N/A	N/A
95% CI	(0.21, 0.79)	(0.24, 0.84)	(0.14, 0.60)	(0.19, 0.69)	(0.06, 0.42)	(0.07, 0.45)		
Diff (%) (BMS-Warf)	-15.3	-14.2	-18.4	-16.7	-21.8	-21.2		
95% CI	(-25.9, -4.2)	(-24.9, -2.9)	(-28.6, -7.8)	(-27.0, -5.1)	(-31.7, -12.3)	(-31.0, -11.6)		
p-value*		0.188			0.132			

N = Number of subjects included in the analysis for each treatment arm
*p-value for dose-response across the 3 QD or acros the 3 BID treatment arms.

A dose response for adjudicated VTE/all cause death rates was observed although this was not statistically significant (p=0.19 qd and p=0.13 bd). All apixaban arms had at least a 21% reduction in VTE/all cause death compared with enoxaparin, and at least 53% compared with warfarin. Events were consistently lower in the bd arms compared with qd (Figure 4).

Figure 4: VTE/All-cause death



Ancillary analyses

The composite endpoint event of proximal DVT/PE or all cause death occurred in 4.6% subjects treated with enoxaparin and in 0-2.7% subjects in the apixaban groups.

Events during follow up period

There was one DVT and two PE (one fatal) during the 30 day follow up period. One PE occurred in the setting of acute infection. The fatality occurred in setting of acute myocardial infarction (in the apixaban 2.5 mg bid group).

PK and PD results

Apixaban exposure was assessed from peak and trough concentrations. There was a dose relationship in both the qd and bd groups and steady state was achieved after about 3 days irrespective of qd or bd dosing.

Dose related increases in INR and PT were observed in both the qd and bd groups and the changes were correlated with PK.

Safety

The primary safety endpoint was bleeding, adjudicated and classified as major, minor or potentially significant non-overt bleeding. Safety was also assessed by review of adverse events (AEs), serious adverse events (SAEs) and laboratory test results.

Bleeding

There was a dose response for total adjudicated bleeding rates in apixaban groups although there were no apparent differences between qd and bd dosing (Figure 5).

Major bleeding events ranged from 0.3-3.3% in the apixaban groups, while none occurred in the enoxaparin or warfarin groups (Figure 6).

Figure 5: Total bleeding rates

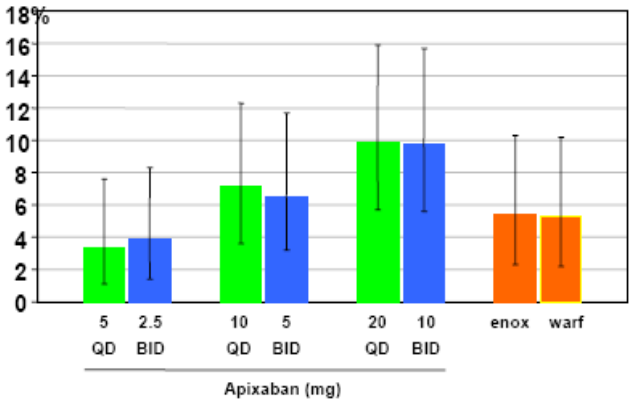
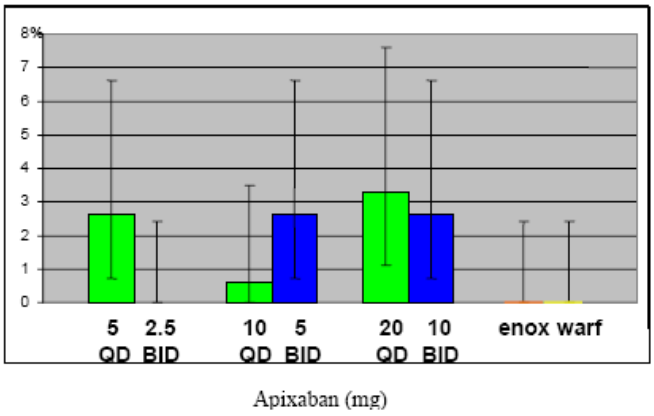


Figure 6: Major bleeding rates



One subject receiving apixaban 10 mg bd had a GI haemorrhage from a gastric ulcer. One subject receiving apixaban 5 mg bd had an event of moderate haematuria. All other major events were haematoma and bruising associated with the knee surgery.

Overall, dose dependent bleeding was apparent for both qd and bd apixaban groups when the composite endpoint of major, minor and potentially significant bleeding was assessed. Event rates ranged from 3.3% at low dose to 9.9% at high dose with enoxaparin 5.4% and warfarin 5.3%.

Overall summary

A dose response trend was observed for the primary endpoint in the apixaban 5, 10 and 20 mg daily groups, with superior efficacy of bd compared with qd dosing apparent at each dose. Efficacy at all doses was numerically superior to enoxaparin 30 mg q12h and to warfarin. An estimated VTE/death event rate of 8.4% for the proposed 2.5 mg bd regimen compared with 13.1% for the 5 mg OD dose. This can be considered clinically meaningful although statistical significance could not be established.

The safety endpoint of bleeding also showed a clear dose response trend although the numbers in each group were too small to establish statistical significance. Bleeding events were more frequent with the higher apixaban daily doses with similar rates for both enoxaparin and warfarin. The estimated relative risk reduction with apixaban 5 mg daily was approximately 30% compared with enoxaparin 30 mg q12h and the major bleeding events were low (range 0.3-3.3%).

The composite endpoint of VTE/all-cause death/major bleed in each group is compared in Table 5. This endpoint combines overall efficacy with the most significant safety concern, major bleeding. Event rates with enoxaparin (15.6%) were lower than with warfarin (26.6%). Event rates for apixaban ranged from 8.4-15% with the results clearly favouring bd dosing versus qd dosing.

Table 5: Summary of bleeding events

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Table 10.2.1B: Summary of Other Adjudicated Events during the Evaluation Period - Primary Subjects and Subjects with Major Bleeding

	Apixaban QD 5mg (N= 100)	Apixaban QD 10mg (N= 106)	Apixaban QD 20mg (N= 114)	Apixaban BID 2.5mg (N= 111)	Apixaban BID 5mg (N= 107)	Apixaban BID 10mg (N= 114)	Enoxaparin (N = 109)	Warfarin (N = 109)
VTE /All cause Death/ Major Bleed, n	15	14	13	11	9	10	17	29
Event rate (%)	15.0	13.2	11.4	9.9	8.4	8.8	15.6	26.6
95% CI	(8.6, 23.5)	(7.4, 21.2)	(6.2, 18.7)	(5.1, 17.0)	(3.9, 15.4)	(4.3, 15.5)	(9.4, 23.8)	(18.6, 35.9)

Discussion and comments

This was an appropriately designed and conducted dose ranging study. Although the study was not powered to show statistically significant differences between groups, the subject numbers were sufficient to demonstrate credible dose response relationships with apixaban for both VTE and bleeding events. All reasonable attempts to limit bias were made. The demographics were similar between treatment groups and the study was double blind with placebo matching of PO and SC treatment. Dosing compliance and investigator follow up of VTE and bleeding events were energetically monitored. All DVT, PE, bleeding and deaths were adjudicated by an experienced ICAC which was blinded to treatment and the study results.

The warfarin arm was open label of necessity which weakens the validity of the data. However warfarin is arguably no longer the gold standard for VTE prevention in orthopaedic surgery and its relevance to this study is open to question. An appropriate additional or alternative comparator might have been enoxaparin 40 mg qd, the dose used in two of the three pivotal Phase III studies, and the dose approved in EU and most other countries outside of North America. No rationale for this omission is apparent.

The dose of enoxaparin in this study was 30 mg q12h, the approved dose in the US. Hypothetically, selection of 40 mg qd, the approved dose elsewhere, would have influenced the risk/benefit relationship, with increased efficacy in favour of apixaban and increased safety in favour of enoxaparin. However, the 2.5 mg bd dose chosen for the Phase III program was clearly the most appropriate on the evidence available if the primary objective was to be met; that is, similar or less bleeding with apixaban with improved or similar efficacy compared to enoxaparin.

The risk of bleeding appeared to be higher in patients given apixaban 20 mg daily or 10 mg bd. However the difference appears small, suggesting that a clinically meaningful safety window might exist in the event of accidental overdose or increased exposure due to drug-drug interactions. This will be discussed in conjunction with the review of the pivotal Phase III studies.

Main (pivotal) studies

CV185047 Pivotal study for TKR surgery

This was a Phase III, randomized, double blind, active controlled (enoxaparin 40 mg qd), parallel group, multicentre study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total knee replacement surgery.

Methods

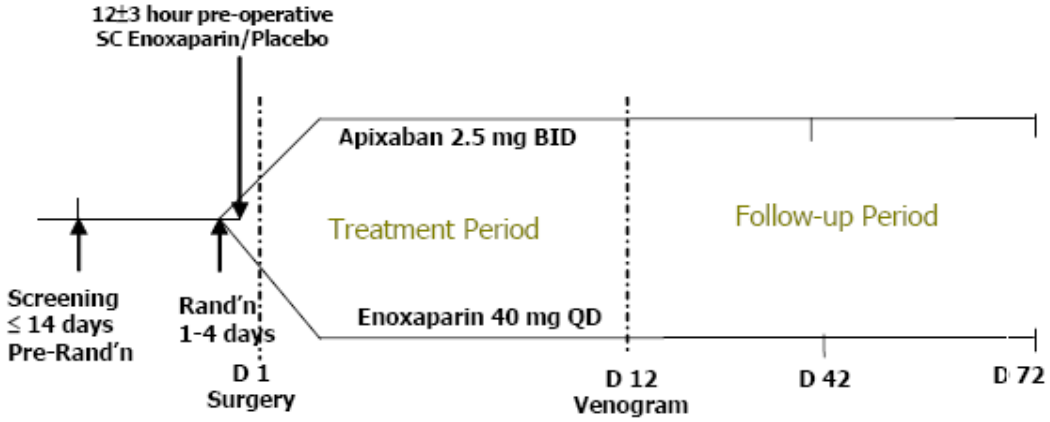
125 centres in 27 countries recruited 3057 randomised subjects undergoing TKR. Centres in US or Canada were excluded because the approved label precluded dosing with

enoxaparin 40 mg qd. Subjects were randomised to receive apixaban 2.5 mg bd PO or matching placebo; or enoxaparin 40 mg qd SC or matching placebo.

Apixaban 2.5 mg qd was the lowest dose evaluated in the Phase II study CV185010. There was a >30% relative risk reduction in VTE and all cause death when compared to enoxaparin, the active comparator used in most DVT prevention trials. There were no major bleeding events and clinically significant bleeding was less than with enoxaparin (given 30 mg q12h).

The study included a screening period starting no earlier than 14 days before randomization; a randomization period of 1-4 days before surgery; a treatment period starting with the first dose of SC study drug given 12 hours before surgery and continued for 11+/-2 days after surgery; and a 60 day follow up period starting after the last dose of the study drug (Figure 7).

Figure 7: Treatment scheme for CV185047



The treatment period started with the first dose of SC medication 12 hours before surgery. The double blind study drug was resumed on the morning after surgery and continued for 11 days. While in hospital, subjects were investigated daily for symptomatic VTE, bleeding events and wound assessment. After discharge, subjects were required to report all AE, VTE and bleeding events to the investigator.

A mandatory bilateral ascending contrast venogram was to be performed 11 days post-surgery and this contributed to the primary study endpoint. Adjudicated symptomatic PE were determined by various techniques including angiography, nuclear ventilation perfusion (V/Q) scan, CT, etc. Follow up visits occurred on Days 30 and 60 after the last dose of the study drug. Subjects were required to report all AE, VTE and bleeding to the investigator. All laboratory assessments were conducted in a central laboratory. Pharmacokinetic and pharmacodynamic endpoints were determined using peak and trough plasma samples, and anti-Factor Xa activity was plotted against apixaban plasma concentrations.

Objectives

The objective of the study was to demonstrate similar or improved efficacy with apixaban compared to enoxaparin, with similar or fewer bleeding events. Other objectives included an analysis of population PK, PK/PD relationships and exposure response relationships.

Study participants

Key inclusion criteria were subjects undergoing unilateral or same day bilateral TKR; and subjects willing and able to undergo bilateral ascending contrast venography.

Key exclusion criteria were bleeding or coagulation disorders; active bleeding or risk of bleeding; active hepatobiliary disease; significant hypertension; significant anaemia, thrombocytopenia or impaired renal function; ALT or AST >2xULN; treatment with medications affecting coagulation or platelet function; and need for ongoing treatment with parenteral or oral anticoagulants.

Before leaving hospital, subjects were instructed on timing and administration of the study drug. Compliance was assessed using review of subject diary cards with tablet and syringe counts. More than 96% of apixaban and enoxaparin subjects achieved compliance defined as >80% of expected drug administration.

Key criteria for discontinuing study medication were withdrawal of informed consent; significant AE, laboratory abnormality or intercurrent illness; signs and/or symptoms suggestive of DVT in either leg, confirmed by ultrasound or venography; signs or symptoms suggestive of PE, confirmed by diagnostic investigations including V/Q scan, CT and pulmonary angiogram; jaundice or significantly raised liver function tests (LFT); SAE requiring the use of anticoagulants or antiplatelet agents; and an increased risk of bleeding complications.

Subjects who prematurely discontinued treatment were followed-up and end of study venography performed whenever possible.

Treatments

Subjects received apixaban 2.5 mg bd PO or matching placebo; and enoxaparin 40 mg qd SC or matching placebo.

Outcomes / endpoints

The primary efficacy endpoint was the composite of all ICAC adjudicated VTE (PE, symptomatic and asymptomatic DVT) and all cause death during the intended treatment period. The key secondary endpoint was the composite of adjudicated asymptomatic and symptomatic DVT, non-fatal PE, and VTE related death during the treatment period. There were multiple other secondary endpoints.

Signs and symptoms of VTE included lower limb DVT: erythema, warmth, pain, swelling or tenderness; and PE: pleuritic chest pain, dyspnoea, cough, haemoptysis, syncope, tachypnoea or tachycardia.

Mandatory adjudication of venography

The objectives of venography were to categorize each subject as:- having no proximal DVT; having proximal DVT; non-evaluable for proximal DVT; having no distal DVT; having distal DVT; or non-evaluable for distal DVT.

The key PK objectives were to characterise the population PK of apixaban; to characterise the relationship between apixaban PK and anti-FXa activity; and to characterise the exposure/response relationship for the primary endpoints.

Statistical considerations

With a total of 3058 subjects randomised, there was >99% power to show NI and 90% power to show superiority at a 1-sided 0.025 level assuming event rates of 11% for apixaban and 16% for enoxaparin. The sample size was based on the assumption that approximately 30% of venograms would be not done or non-evaluable (numbers based on the Phase II study CV185010, and other published DVT trials). Non-inferiority of apixaban compared with enoxaparin was assumed if the upper bound of the two sided 95% CI for the RR was <1.25; and if the upper bound of the two sided 95% CI for the risk difference was <5.6%.

Subjects were centrally randomized 1-4 days before surgery. They were randomized 1:1 to receive either apixaban 2.5 mg tablets or matching placebo; and enoxaparin 40 mg injection or matching placebo. The subjects, investigators and adjudicating committee (ICAC) were all blind to the randomisation schedule.

Results

Subjects were recruited from numerous countries and regions with >72% from Europe. The groups were evenly balanced with 1528 subjects randomized to apixaban 2.5 mg bd and 1529 subjects randomized to enoxaparin 40 mg qd.

Overall, 91.1% of subjects in each group completed the treatment period. Withdrawal of consent and AE were the main reasons for withdrawal from the study. Evaluable subjects were 59.4% with apixaban and 60.2% with enoxaparin.

The median age in both groups was 67 years and approximately 20% were >75 years. Over 70% were female and almost 80% were White. About 73% of subjects had no risk factors. In those having risk factors, the commonest were previous lower limb orthopaedic surgery and/or previous VTE events and there were no differences between treatment groups. Approximately 98% of subjects were treated in each group, and approximately 60% in each group were evaluable for the primary endpoint.

Primary efficacy analysis

The event rate with apixaban [14.88% (95% CI: 12.71-17.36)] was statistically significantly lower and compared with enoxaparin [24.76% (95% CI: 22.07-27.66)] based on the per protocol analysis. The relative risk (RR) in favour of apixaban was 0.60 (95% CI: 0.50-0.73) and the one-sided p-value for non-inferiority on RR was <0.0001. The one-sided p-value for superiority on RR was <0.0001.

Events during the evaluation period

The incidence of all VTE/all-cause deaths was 15.06% in the apixaban group and 24.37% in the enoxaparin with RR 0.62 in favour of apixaban. The results were similar in evaluable subjects (p<0.0001) (Table 6).

Table 6: Summary of adjudicated VTE events and all cause death

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Table 7.2B: Summary of Adjudicated VTE Events and All-Cause Death with Onset During the Intended Treatment Period - Evaluable Subjects

	Apix 2.5 mg BID N=907	Enox 40 mg QD N=921
ALL VTE/ALL-CAUSE DEATH, N	135	228
EVENT RATE (%)	14.88	24.76
95% CI FOR EVENT RATE	(12.71, 17.36)	(22.07, 27.66)
RELATIVE RISK (APIX/ENOX)	0.60	
95% CI FOR RELATIVE RISK	(0.50, 0.73)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001**	
RISK DIFFERENCE (%) (APIX-ENOX)	-9.83	
95% CI FOR RISK DIFFERENCE	(-13.45, -6.21)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON DIFFERENCE	<0.0001*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON DIFFERENCE	<0.0001**	
ONE-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001**	

The principal secondary endpoint of adjudicated proximal DVT, non-fatal PE and VTE related death during the treatment period occurred in 1.09% apixaban subjects and 2.17% with enoxaparin with RR 0.50 (p<0.019) in favour of apixaban.

Most of the multiple secondary endpoint events occurred less frequently with apixaban than with enoxaparin with the exception of fatal and non-fatal PE, 4 (0.26%) in the apixaban group versus none in the enoxaparin group.

Events during follow up period

Event rates in the 60 day follow up period were few with three PE (one fatal) in the apixaban group (0.21%) and one in the enoxaparin group (0.07%).

Ancillary analyses

Event rates were compared in sub-groups defined by age, gender, geographical region, BMI, and race. The effect of apixaban relative to enoxaparin on the primary efficacy endpoint was similar within each sub-group compared with that observed in the overall population. The relative risk ratio (RRR) in sub-groups ranged from 28-57%.

PK profiles were obtained in four apixaban subjects and they were similar to those obtained in the Phase II study CV185010. There was a close relationship between apixaban plasma concentrations and anti-FXa activity.

Comments

In this study, apixaban 2.5 mg bd showed consistently superior efficacy compared with enoxaparin 40 mg qd for the primary and secondary endpoints. These differences were highly statistically significant and clinically meaningful.

Event rates for adjudicated proximal DVT, non-fatal PE, and VTE related death were 1.1% for apixaban and 2.2% for enoxaparin, a RRR of 50%. However, fatal and non-fatal PE were more frequent in the apixaban group. These results are not consistent but may possibly be related to the small number of events overall.

A potential methodological problem was missing or non-evaluable venograms, 36% and 35% in the apixaban and enoxaparin groups respectively. This frequency is higher than 30% recorded in most similarly designed studies but it is unlikely to have biased the conclusions. The two treatment groups were evenly balanced for demographics and baseline characteristics; the study was double blind; and the reasons for missing or non-evaluable venograms were similar in each group.

CV185035 Pivotal study for THR

This was a Phase III, randomized, double blind, active controlled, parallel group, multicentre study to evaluate the safety and efficacy of apixaban in subjects undergoing elective total hip replacement surgery (The Advance-3 study apixaban dosed orally versus anticoagulation with injectable enoxaparin to prevent venous thromboembolism).

Methods

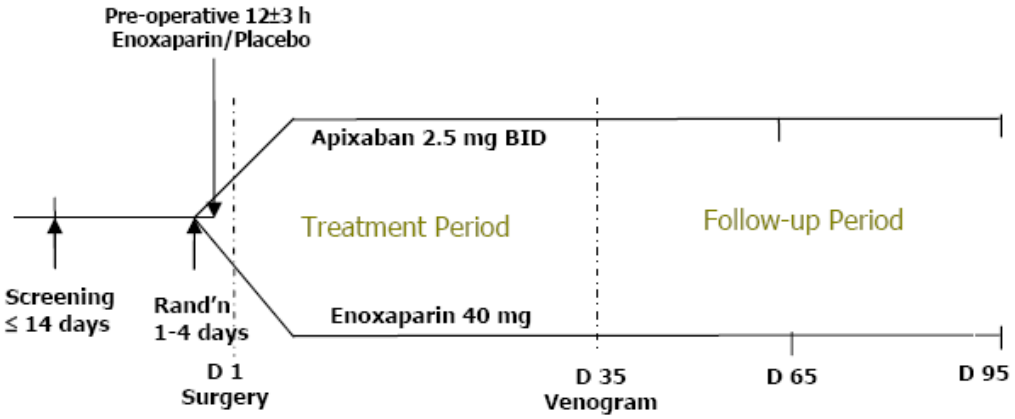
The study was designed to compare the safety and efficacy of oral apixaban 2.5 mg bd with SC enoxaparin 40 mg qd in subjects undergoing elective THR surgery.

Apixaban 2.5 mg bd was the lowest dose evaluated in the Phase II dose ranging study CV185010. It showed a >30% RRR in VTE and all cause death compared with enoxaparin and a >50% reduction compared with warfarin. There were no major bleeding events and clinically significant bleeding events were also lower than with enoxaparin. Enoxaparin 40 mg qd was chosen because it is a widely used active control in similar DVT prevention studies.

The first dose of enoxaparin or placebo was to be given 12+/-3 hours before surgery and the first dose of apixaban or placebo was to be given 12-24 hours after wound closure.

There were four study periods: a screening period of not more than 14 days; a randomization period 1-4 days before surgery; a treatment period, study drug or placebo was started 12+/-3 hours before surgery through to 35+/- 3 days after surgery; and a follow up period of 60+/-5 days, starting after the last dose of the study drug (Figure 8).

Figure 8: Treatment scheme for CV185035



While hospitalised, subjects were evaluated daily for symptomatic VTE and bleeding events. Eleven days and 34 days after surgery, the subjects were asked to report to the investigator all AE, signs and symptoms suggestive of VTE and any bleeding events experienced since the last visit. Subjects with signs and/or symptoms of VTE were to return to the clinic for appropriate diagnostic investigations. On the 34 day visit, subjects who remained asymptomatic for VTE underwent mandatory bilateral ascending contrast venography.

Objectives

The primary objective was to compare the effects of treatment on the composite endpoint of asymptomatic and symptomatic DVT, non-fatal PE, and all cause death in subjects undergoing THR. The key secondary objective was to compare treatment effects on the composite endpoint of proximal DVT, non-fatal PE and VTE related death at the end of the treatment period.

The key safety objective was to compare the effects of treatment on: major bleeding; the composite of major and clinically relevant non-major (CRNM) bleeding; clinically relevant non-major bleeding; and overall safety and tolerability. The PK objectives were to characterize population PK, PK variability, PK/PD relationships, and exposure/response relationships for clinically important endpoints.

Study participants

Key inclusion criteria were: subjects undergoing elective total hip replacement; and subjects willing and able to undergo bilateral ascending contrast venography. Key exclusion criteria were similar to those in CV185047 (see above).

Treatments

Subjects received apixaban 2.5 mg bd PO or matching placebo; and enoxaparin 40 mg qd SC or matching placebo.

Outcome/endpoints

The primary efficacy endpoint was the composite of all adjudicated VTE (asymptomatic and symptomatic DVT, PE) and all cause death during the treatment period in subjects undergoing THR surgery. The key secondary endpoint was the composite of adjudicated

asymptomatic and symptomatic proximal DVT, non-fatal PE, and VTE related death during the treatment period.

There were numerous other composite and single secondary endpoints similar to those in CV185047.

Statistical considerations

The event rates for the primary and key secondary endpoints were estimated after 80% of the initial target number of 4022 subjects was randomized. The sample size was then increased to 5406 to power the NI test on the primary efficacy endpoint. With 5406 randomized subjects, there was 90% power to establish NI at the 0.025 level if the true event rates were 2.72% in the apixaban group and 3.88% in the enoxaparin group. The assumptions for the sample size calculation were based on a composite rate of 30% for "not done" or "non-evaluable" venograms for proximal and distal DVT, and a composite rate of 20% for "not done" or "non-evaluable" venograms for proximal DVT. These rates were based on data from the Phase II dose ranging study CV185010 and similar published trials, and agreed by the EU and US regulatory authorities.

Subjects were centrally randomised 1:1 to receive apixaban 2.5 mg tablets or matching placebo; and enoxaparin 40 mg injection or matching placebo. All subjects, investigators and the ICAC were blind to the study treatment for the duration of the study.

Study participants

A total of 160 centres in 21 countries (mainly in North America, Russia and Eastern Europe) recruited 5407 subjects who were randomized to double blind treatment. Study completion and withdrawal rates were comparable with approximately 90% of subjects completing the treatment period. Exposure was similar between groups with approximately 84% receiving treatment for 32-38 days. Approximately 98% of subjects in each group received a post-surgery dose; approximately 86% received the first dose in the protocol defined window of 12-24 hours post-surgery. VTE risk factors were comparable in each group. Approximately 32% of subjects had one or more risk factors, mainly previous lower limb orthopaedic surgery and/or previous VTE events.

There was a similar frequency of significant protocol deviations in each group, mainly incorrect dose timing, incorrect treatment assignment and use of prohibited concomitant medications. There were 225 (8.3%) randomized subjects with significant deviations in the apixaban group, and 222 (8.2%) in the enoxaparin group.

Compliance assessments and withdrawal criteria were as described for study CV185047.

Subject demographics were similar in each group. Median age was 61 years with approximately 12% older than 75 years. Approximately 53% were female and over 90% were white. Approximately 88% of subjects had normal renal function or only mild impairment (CrCl 30-60 mL/min).

Efficacy endpoints were analysed during the intended treatment period and during the intended follow up period. Approximately 68% of subjects in each group were evaluable, and approximately 72% in each group were evaluable for the primary endpoint. The number of subjects excluded from the primary efficacy analysis because of missing or non-evaluable venograms was 28% in the apixaban group and 29% in the enoxaparin group.

Outcomes and estimation

Primary efficacy event rates were 1.30% for apixaban and 3.72% for enoxaparin ($p<0.00001$) with an observed RR in favour of apixaban of 0.35, based on the per protocol analysis (Table 7). Apixaban was also superior to enoxaparin for the key secondary

endpoint. Event rates for apixaban were 0.45% and 1.14% for enoxaparin (p=0.0054) with a RRR of 60%. The NI criteria for the primary and secondary endpoints were also met, p<0.00001 for both analyses.

Table 7: Summary of adjudicated VTE events and all cause death

Apixaban
BMS-562247

CV185035
Phase 3 Final Clinical Study Report

Table 7.2B: Summary of Adjudicated VTE Events and All-Cause Death with Onset During the Intended Treatment Period - Evaluable Subjects

	Apix 2.5 mg BID N=1850	Enox 40 mg QD N=1829
ALL VTE/ALL-CAUSE DEATH, N	24	68
EVENT RATE (%)	1.30	3.72
95% CI FOR EVENT RATE	(0.87, 1.94)	(2.94, 4.70)
RELATIVE RISK (APIX/ENOX)	0.35	
95% CI FOR RELATIVE RISK	(0.20, 0.54)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	<0.0001**	
RISK DIFFERENCE (%) (APIX-ENOX)	-2.42	
95% CI FOR RISK DIFFERENCE	(-3.49,- 1.44)	
ONE-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001*	
TWO-SIDED P-VALUE FOR SUPERIORITY TEST ON RR	<0.0001**	

* denotes that the result is statistically significant at the one-sided 0.025 level
** denotes that the result is statistically significant at the two-sided 0.05 level

There was a small number of symptomatic VTE events and death: there were three deaths (0.11%) in the apixaban group and one (0.04%) following enoxaparin; and there were three PE in the apixaban group (one fatal) and 5 in the enoxaparin group.

Follow up period

During the 60 day follow up period, there were no PE in the apixaban group and 4 in the enoxaparin group. There were two deaths in the apixaban group and one following enoxaparin.

PK/PD results

PK profiles were measured on Day 3 for population PK and to estimate exposure/response relationships. Peak and trough anti-FXa activity was estimated for both apixaban and enoxaparin. There was a good correlation between peak and trough anti-FXa activity.

Summary of efficacy

Apixaban was significantly superior to enoxaparin for the primary and key secondary endpoints with RRR of 64% and 60% respectively in patients undergoing THR. Trends in favour of apixaban were also noted for most of the individual components of the composite scores. Non-inferiority and superiority of apixaban compared with enoxaparin was shown for VTEp in patients undergoing THR.

Clinical studies in special populations

Subgroups defined by geographic region, age, gender, race, weight, BMI, level of renal impairment, type of surgery and number of risk factors were identified for statistical analysis *a priori* in the protocols for the pivotal studies.

Subgroup analyses were performed to detect any marked differences from the overall study; and to see if any such differences should lead to dose modification. Overall there

were no substantial differences in the subgroups compared with the total population in the individual or pooled pivotal studies.

In the pivotal THR study CV185035, the results within each subgroup were consistent with the overall study results. The study was not powered for subgroup analyses but the estimated risk reduction (RR) was <1 in favour of apixaban within most subgroups**.** In the pivotal TKR study CV185047, the results were similar and the only subgroups with RR ≥ 1 were those with small numbers.

Treatment by subgroup interaction analyses for the primary efficacy endpoint were conducted and none of the grouping variables generated p-values <0.1 except age (p< 0.094) in the pooled pivotal studies. In summary there was no evidence to suggest that dose modification is required in subgroups based on the primary efficacy endpoint.

The most important safety parameter is bleeding but there was no subgroup in which bleeding rates in apixaban subjects were different from those in the enoxaparin group.

In the pivotal THR study CV185035, the overall results were consistent with those of the total study population. For major bleeding, the estimated risk difference (RD) ranged from -1% (favouring apixaban) to +1% (favouring enoxaparin) for 20 of 24 subgroups and the differences were minor in the remaining four subgroups. The results for the composite endpoint of major or CRNM bleeding were similar with the estimated RD below zero (favouring apixaban) for 16 of the 24 subgroups. For all bleeding, the estimated RD was below zero for 19 of the 24 subgroups.

In the pivotal TKR study CV185047, the results within subgroups were consistent with the overall study. For major bleeding, the estimated RD ranged from -1% to +1% in 17 of the 24 subgroups and differences in the remaining six subgroups were minor. For the composite endpoint of major or CRNM bleeding, the estimated RD was below zero in 18 of the 24 subgroups; and for all bleeding it was below zero in 18 of the 24 subgroups.

There was no convincing evidence to suggest an increased risk of bleeding in any subgroup treated with apixaban in the pivotal studies in which the comparator dose of enoxaparin was 40 mg qd. There is no evidence to suggest that dose reduction is required to reduce the risk of bleeding in any subgroup.

Analysis performed across trials (pooled analyses and meta-analysis)

In the pivotal studies, CV185035 and CV185047 there were marked reductions in the primary composite endpoint of all VTE/all cause death (Table 8). The NI criteria for the primary endpoint were met. RRR was 64% for THR in favour of apixaban versus enoxaparin 40 mg qd and 38% for TKR: these reductions were both highly significant (p<0.0001) and clinically meaningful.

Table 8: All VTE/all cause death - CV185035 and CV185047

Apixaban
BMS-562247

Module 2.5 Clinical Overview
Prevention of Venous Thromboembolic Events

All Venous Thromboembolism/All-cause Death (Studies CV185035 and CV185047)

	Study CV185035 (ADVANCE-3) Hip Replacement			Study CV185047 (ADVANCE-2) Knee Replacement		
	Apixaban	Enoxaparin	P-value	Apixaban	Enoxaparin	P-value
Dose	2.5 mg BID PO	40 mg QD SC		2.5 mg BID PO	40 mg QD SC	
Duration of Treatment	35 ± 3 days	35 ± 3 days		12 ± 2 days	12 ± 2 days	
No. of Events/Subjects	27/1949	74/1917		147/976	243/997	
Event Rate	1.39%	3.86%		15.06%	24.37%	
Relative Risk	0.36		< 0.0001	0.62		< 0.0001
95% CI	(0.22, 0.54)			(0.51, 0.74)		

BID = twice daily, CI = confidence interval, PO = orally, QD = once daily, SC = subcutaneously

For the main secondary endpoint of major VTE (proximal DVT, non-fatal PE and VTE-related death, the RRR was 60% for THR (p= 0.0107) and 50% for TKR (p= 0.0373) in favour of apixaban (Table 9).

Table 9: Major VTE - CV185035 and CV185047

Major Venous Thromboembolism (Studies CV185035 and CV185047)

	Study CV185035 (ADVANCE-3) Hip Replacement			Study CV185047 (ADVANCE-2) Knee Replacement		
	Apixaban	Enoxaparin	P-value	Apixaban	Enoxaparin	P-value
Dose	2.5 mg BID PO	40 mg QD SC		2.5 mg BID PO	40 mg QD SC	
Duration of Treatment	35 ± 3 days	35 ± 3 days		12 ± 2 days	12 ± 2 days	
No. of Events/Subjects	10/2199	25/2195		13/1195	26/1199	
Event Rate	0.45%	1.14%		1.09%	2.17%	
Relative Risk	0.40		0.0107	0.50		0.0373
95% CI	(0.15, 0.80)			(0.26, 0.97)		

BID = twice daily, CI = confidence interval, PO = orally, QD = once daily, SC = subcutaneously

The incidence of major VTE, PE and deaths were low and inconsistent across studies.

Although the dose ranging study CV185010 in TKR was not powered to detect a difference in efficacy, apixaban at all doses appeared superior to enoxaparin despite the 50% higher US approved dose of 30 mg q12h.

Supportive study

CV185034 was a Phase III randomized, double blind, active controlled (enoxaparin), parallel group, multicentre study to evaluate the safety and efficacy of oral apixaban in subjects undergoing elective total knee replacement surgery.

Methods

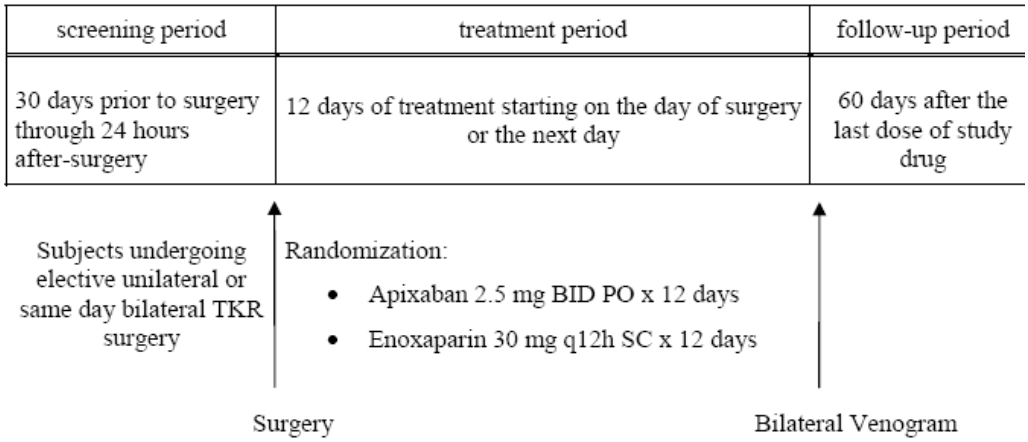
The study was designed to compare the safety and efficacy of apixaban 2.5 mg bd with SC enoxaparin 30 mg q12h in subjects undergoing TKR.

The dose of enoxaparin selected for this study, 30 mg q12h SC, is approved in the US for TKR, and was also used as the active comparator in the dose ranging study.

There were three study periods (Figure 9):

- A 30 day screening period with randomisation occurring after surgery
- A 12+/-2 day treatment period, starting on the day of surgery or the next day
- A 60 day follow up period starting on the last day of the study drug

Figure 9: Treatment scheme for CV185034



The study used matching placebos for the PO and SC treatments. The subjects and investigators were all blind to the randomization code. All DVT, PE, bleeding events, deaths and significant laboratory abnormalities were reviewed and adjudicated by the ICAC.

The treatment period started with the first dose of study of PO or SC treatment started 12—24 hours after wound closure (a time based on the US enoxaparin label) and was continued for 12+/-2 days. While in hospital, there was a daily wound assessment and subjects were evaluated daily by the investigator for bleeding and symptomatic VTE. Following discharge, subjects were required to report all AE, SAE, VTE and bleeding events to the investigator. The investigator was required to immediately investigate signs or symptoms suggestive of VTE with appropriate diagnostic tests such as ultrasound or venography.

A mandatory bilateral ascending venogram was performed at the end of the treatment period in all subjects who were asymptomatic for VTE, and this contributed to the primary composite endpoint. Symptoms or signs of PE were investigated by procedures such as V/Q scan or pulmonary angiography. The results of the VTE and PE investigations were then adjudicated by the ICAC.

Objectives

The objective of the study was to demonstrate reduced bleeding events with apixaban, with comparable or superior efficacy to enoxaparin.

Study participants

Inclusion/exclusion criteria were similar to those of the dose ranging and pivotal studies.

Treatments

Subjects received apixaban 2.5 mg tablets bd or enoxaparin 30 mg SC q12h.

Outcomes/endpoints

The primary efficacy objective was to compare the effect of apixaban 2.5 mg bd and enoxaparin 30 mg SC q12h on a composite VTE endpoint consisting of asymptomatic and

symptomatic DVT, non-fatal PE and all cause death after 12+/-2 days of treatment in subjects undergoing TKR.

The key secondary endpoint was the composite of adjudicated proximal DVT, non-fatal PE and all cause death during the treatment period. Several other secondary end points assessed distal versus proximal DVT, symptomatic versus asymptomatic DVT and VTE, and the treated versus follow up periods.

Statistical considerations

With a planned total of 3058 randomized subjects, there was 99% power to establish non-inferiority and 90% power to demonstrate superiority if the true event rates were 11.2% and 16% in the apixaban and enoxaparin groups respectively.

The gold standard for diagnosing asymptomatic DVT in both US and Europe is bilateral ascending contrast venography. In CV185010 and similar published trials, the incidence of venography 'not done', 'missing' or 'non-evaluable' was about 30%. This rate was assumed a priori for both the non-inferiority and superiority analyses.

The primary efficacy analyses were performed on the randomized and evaluable data sets. Non-inferiority of apixaban compared with enoxaparin was assumed if both the following conditions were met:

- Upper bound of the two sided 95% CI for the RR <1.25
- Upper bound of the two sided 95% CI for the risk difference of <5.6%

Superiority of apixaban compared with enoxaparin was assessed if the non-inferiority criteria were met.

Subjects were randomised 1:1 to receive:

- Apixaban 2.5 mg tablets or matching placebo, and
- Enoxaparin 40 mg injection or matching placebo.

All subjects, investigators and the ICAC were blind to the treatments for the duration of the study.

Results

A total of 129 centres in 14 countries recruited a total of 3195 randomized subjects (apixaban 1599 and enoxaparin 1596); 3184 subjects were treated with blinded study drug and 2287 (apixaban 1157 and enoxaparin 1130) were included in the primary efficacy analysis.

Discontinuation rates from the treatment period were 5.6% with apixaban and 6.7% for enoxaparin. Study discontinuations due to AE were also comparable, 3.8% with apixaban and 3.6% with enoxaparin.

Most subjects were >65 years, 62% were female and almost 95% were White. No subjects with severe renal impairment (CrCl <30 mL/min) were recruited but approximately 12% of subjects had moderate impairment (CrCl 30-60 mL/min).

Significant protocol deviations occurred in 6.1% of the apixaban group and 7.7% of the enoxaparin group. The proportion of subjects with deviations likely to affect the primary endpoint was 4.8% in the apixaban group and 6.0% in the enoxaparin group. These were excluded from the evaluable subjects' data set.

Compliance was assessed by tablet count, syringe count and review of the daily diaries. More than 98% subjects in each group were >80% compliant with randomized treatment.

More than 99% of randomized subjects received at least one dose of the study drug. Exposure from first to last day of blinded treatment averaged 11.7 days for apixaban and 11.6 for enoxaparin, with approximately 88% in each group receiving 10-14 days treatment.

Approximately 94% subjects in each group received the first dose of study medication within the 12-24 hour post-operative time window.

Study therapy was withdrawn immediately for reasons similar to those in the dose ranging and pivotal studies.

Outcomes and estimation

The incidence of the primary efficacy endpoint was 8.99% for apixaban and 8.85% for enoxaparin during the treatment period (Table 10). The observed RR of apixaban versus enoxaparin was 1.02 but this did not meet one of the two non-inferiority endpoint criteria. The risk difference was 2.44% compared with the upper bound of the 95% CI <5.6%. However the upper bound of the 95% CI for the RR was 1.32 compared with the protocol criterion of <1.25.

Table 10: Summary of adjudicated VTE events and all cause death

Apixaban CV185034
BMS-562247 Phase 3 CSR

: Summary of Adjudicated VTE Events and All-Cause Death with Onset during the Intended Treatment Period - Primary Subjects

	Apix 2.5 mg BID N=1157	Enox 30 mg q12h N=1130
ALL VTE/ALL-CAUSE DEATH, N	104	100
EVENT RATE (%)	8.99	8.85
95% CI FOR EVENT RATE	(7.47, 10.75)	(7.33, 10.66)
RELATIVE RISK (APIX/ENOX)	1.02	
95% CI FOR RELATIVE RISK	(0.78, 1.32)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON RR	0.0635	
RISK DIFFERENCE (%) (APIX-ENOX)	0.11	
95% CI FOR RISK DIFFERENCE	(-2.22, 2.44)	
ONE-SIDED P-VALUE FOR NON-INFERIORITY TEST ON DIFFERENCE	<0.0001*	

* If one-sided p-value is less than 0.025, then a '*' will be put after the actual p-value to show statistically significant result
** Perform the superiority test only if upper bound for 95% CI for Relative Risk is less then 1.25 and upper bound for 95% CI for Risk Difference is less then 5.6%. If one-sided p-value is less then 0.025, then a '*' will be put after the actual p-value to show statistically significant result

Overall 442 (27.6%) subjects in the apixaban group and 466 (29.2%) in the enoxaparin group were excluded from the primary efficacy analysis because of missing or non-evaluable end of treatment venograms. This was similar to the expected 30% non-evaluability rate used in the sample size calculation.

The event rate for the secondary endpoint of proximal DVT, non-fatal PE and all cause death was 2.05% for apixaban and 1.64% for enoxaparin. The difference between treatment groups was not statistically significant.

Individual efficacy endpoints were comparable in each group:

- All cause death in three subjects in each group (0.19%)
- Two subjects had a fatal PE in the apixaban group and none with enoxaparin

- PE (fatal or non-fatal) occurred in 16 (1%) subjects with apixaban and 7 (0.44%) with enoxaparin.
- All DVT occurred in 89 (7.79%) subjects with apixaban and 92 (8.2%) with enoxaparin
- Proximal DVT occurred in 9 (0.72%) subjects with apixaban and 11 (0.91%) with enoxaparin
- During the intended follow up period, PE (fatal and non-fatal) occurred in one subject (0.06%) following apixaban and 5 subjects (0.32%) who received enoxaparin

Ancillary analyses

Subgroups defined by gender, age, weight, BMI, renal function and ethnicity were analysed and compared with the overall treatment population. There were no differences in the incidence of primary efficacy events in any subgroup compared with the general population.

Non-supportive study

APPRAISE-2 (CV185068) was a Phase III, randomized, double blind evaluation of the safety and efficacy of apixaban in subjects with a recent acute coronary syndrome.

Methods

Approximately 1000 centres in approximately 40 countries were to recruit approximately 10,800 subjects with acute coronary syndrome (ACS). Subjects were randomized 1:1 to receive either apixaban or placebo.

The selected dose of apixaban 5 mg bd was based on the balance of safety and efficacy in the preceding study APPRAISE-1. All subjects received standard post-ACS care and were required to receive single or dual antiplatelet therapy based on investigator discretion. The first dose of the study drug was to be administered as soon as possible after ACS for an average treatment period of 28 months determined by the time required to accrue 938 primary efficacy outcomes events.

Objectives

The objective of the study was to determine if apixaban is superior to placebo for preventing the composite of cardiovascular death, myocardial infarction, or ischaemic stroke, in subjects with recent ACS.

Treatments

Subjects received oral apixaban 5 mg bd or matching placebo. Compliance with treatment was based on study drug tablet count, with its importance reinforced at each scheduled visit. Study drug interruption was permitted for significant AE or laboratory abnormalities, for bleeding or for invasive procedures. The study drug was discontinued at investigator discretion or if consent was withdrawn.

Outcomes/Endpoints

The primary efficacy endpoint was to determine if apixaban is superior to placebo for preventing the composite of cardiovascular death, myocardial infarction, or ischaemic stroke in subjects with recent ACS. The secondary objectives were to determine if apixaban is superior to placebo for a variety of composite endpoints, including cardiovascular death, myocardial infarction, unstable angina, ischaemic stroke and fatal bleeding; to compare apixaban and placebo in sub-populations such as subjects with diabetes mellitus, subjects receiving single or dual anti-platelet therapy, and subjects undergoing PCI; and to compare the effects of apixaban and placebo on the incidence of major bleeding.

Statistical considerations

With 938 subjects having the confirmed primary efficacy endpoint, the study had 80% power to detect a 20% risk reduction of apixaban versus placebo. With an accrual period of 2 years, an average follow up of 28 months and assuming a primary efficacy event rate of 8 events per hundred subject years, a total of 10,800 subjects randomized in a 1:1 ratio was required to receive the desired number of events.

On 14 November 2010, the Data Monitoring Committee stopped the study due to excess bleeding events with apixaban. No further subjects were enrolled and the study drug was discontinued in all subjects entered into the trial at that point. The trial had enrolled 7048 subjects out of the planned total of 10,800. There were 412 primary endpoints (cardiovascular death, non-fatal MI and non-fatal ischaemic stroke), compared with a planned total of 938 to detect a 20% event reduction.

Results

The data reviewed here are those presented to the DMC and which led to study discontinuation. Analysis is continuing and the final study report was not available at the time of the clinical evaluation. However, in the opinion of the sponsor, it is unlikely that results reported after final database lock will be qualitatively different. Results presented below compare placebo (Group A) and apixaban 5 mg bd (Group B).

A total of 7048 subjects were recruited from 40 countries worldwide. Inclusion/exclusion eligibility criteria were not met in 1.6% of subjects treated with placebo and in 1.8% of subjects receiving apixaban. Study withdrawals and treatment discontinuations were similar in each group (28.3% with placebo and 31.5% with apixaban). Withdrawals due to AEs were 9.4% with placebo and 12.4% with apixaban.

Median age in both groups was 67 years and approximately 58% were >65 years. Approximately 68% were male and 75% were Caucasian. More than 77% of subjects were hypertensive, almost 50% were diabetic and approximately 20% were current smokers. Most (97.8%) subjects in each group received concomitant aspirin; >84% received clopidogrel; and approximately 83% received a combination of aspirin and clopidogrel.

Outcomes

In the data considered by the DMC, the primary endpoint of cardiovascular death, MI and ischaemic stroke was reported in 212 subjects in the placebo group and 200 subjects in the apixaban group. An approximate power calculation suggested that there was a 50% chance of achieving a statistically significant outcome if the planned 938 primary events were captured. However the projected difference in event rates would be 6% rather than the planned difference of 20%. There were minor differences in individual endpoints such as non-fatal MI and stroke. However, the Kaplan-Meier plot for the composite primary endpoint fails to show any benefit for apixaban compared with placebo over time.

Comment

The risk of arteriothrombotic events such as MI, stroke or death due to cardiovascular disease is up to 10% in the first year following ACS, despite optimal medical care including aspirin and clopidogrel. The APPRAISE-2 study was designed to improve efficacy without excessive bleeding when added to standard care in these high risk patients. Standard care in CV185068 included single or dual anti-platelet therapy at the discretion of the investigator. All patients were required to have at least two risk factors for a CV event and all were required to receive at least one anti-platelet therapy.

Evaluator's overall conclusions on clinical efficacy

In two pivotal Phase III studies, apixaban 2.5 mg bd significantly reduced (a) all VTE/all cause death and (b) proximal DVT, non-fatal PE and VTE related death compared to enoxaparin 40 mg qd in both TKR and THR. The RRR of between 50-64% for the various endpoints was highly statistically significant and clinically meaningful.

In a supportive Phase III study in TKR, efficacy with apixaban 2.5 mg bd was similar to enoxaparin 30 mg q12h, a predictable outcome as the comparator dose of enoxaparin was 50% higher than that employed in the pivotal studies.

Despite the clear evidence for superior efficacy in favour of apixaban, there was no statistical difference between treatments on the frequency of non-fatal and fatal PE. During the intended treatment period, there were 12 fatal or non-fatal PE in the two pivotal studies in which the enoxaparin dose was 40 mg qd. The observed event rates for PE were lower for apixaban than enoxaparin in the THR study CV185035 (3 on apixaban and 5 on enoxaparin), but the reverse occurred in the TKR study CV185047 (4 on apixaban and none on enoxaparin). These rates are low and the differences are not clinically meaningful.

Distal and proximal DVT precipitate PE and this linked pathophysiology of VTE disease predicts that risk reduction for all events would be similar following VTEp. However, PE is often not clinically apparent and screening for asymptomatic events was not a protocol requirement. Numerous asymptomatic events might not have been detected in these studies and it is possible that this skewed the data for this important endpoint.

Symptomatic PE numbers were low in each group, unexpectedly so in CV185034 in which the comparator was enoxaparin 30 mg q12h. PE occurred in 16 subjects on apixaban and in 7 subjects on enoxaparin during the treatment period whereas the opposite trend occurred during the follow up period (one PE occurred in the apixaban group and five in the enoxaparin group). The PE rate in the enoxaparin group (which used 30 mg q12h) was higher than in the pivotal studies (which used 40 mg qd) and there is no clear explanation for this discordance.

The numerical advantage in favour of enoxaparin might be real or a chance finding and the sponsor has addressed both hypotheses in the sponsor's *Clinical Overview*. The evaluator agreed that it is more likely to be a chance statistical anomaly for two reasons. Firstly, event rates were very low in all four studies and the likelihood of having chance findings in this circumstance is high. Secondly, there is no plausible explanation for higher PE rates following apixaban, when event rates for DVT and proximal DVT were approximately twofold lower than enoxaparin.

Safety

Introduction

Safety information relating to the proposed indication is drawn from a dose ranging study in TKR, two pivotal Phase III studies in TKR and THR, and a supportive study in TKR. The Phase II dose ranging study (CV185010) and the Phase III study (CV185034) compared apixaban 2.5 mg bd with enoxaparin 30 mg q12h post-surgery, which is the approved dose regimen in the US for TKR. In the pivotal studies (CV185035 and CV185047) the enoxaparin comparator dose was 40 mg qd given 9-15 hours before surgery, the regimen approved in EU and ROW. Apixaban was administered 12-24 hours post-surgery. The duration of treatment was 12 days for TKR and 35 days for THR in keeping with standard practice. All Phase III studies had a 60 day follow up period starting after the last dose of study medication. A total of 11,828 subjects received apixaban 2.5 mg bd or enoxaparin in

four orthopaedic VTEp studies. A total of more than 39,000 subjects have been treated with apixaban in 15 completed or ongoing Phase II and III studies for other indications.

Data were presented for all studies pooled, comparing apixaban with both doses of enoxaparin; the two pooled pivotal Phase III studies comparing apixaban with enoxaparin 40 mg qd; and individual study data where appropriate.

The primary safety endpoint for all four VTEp studies was bleeding defined as adjudicated major bleeding using criteria adapted from International Society on Thrombosis and Hemostasis (ISTH) guidelines; a composite of adjudicated major bleeding and CRNM bleeding; and all bleeding endpoints (adjudicated or reported by the investigator).[11]

All acute clinically overt bleeding events were adjudicated by the same ICAC, an experienced panel of physicians who were blind to the order of randomised treatment. Subjects were evaluated daily by the investigator during their hospital admission while all AE following hospital discharge were self recorded by the subjects.

Vital signs, clinical chemistry and haematology panels were performed at screening, randomisation, the day of surgery, the first three days post-surgery, on the last day of treatment and at the follow up visits.

Patient exposure

Overall, 11,828 subjects received apixaban 2.5 mg bd (5,924) or enoxaparin 40 mg qd (4,167) or enoxaparin 30 mg q12h (1,737). The extent of exposure was similar in both groups (Table 11). Taking dosing interruptions into account, 46% of the subjects in the TKR studies received the study drug for 10-14 days as per protocol, while 38% received study drug for 32-38 days in the THR study. However, there were no significant differences between the treatment groups or in subgroups.

Table 11: Overview of duration of exposure

Apixaban
BMS-562247

Module 2.7.4 Summary of Clinical Safety
Prevention of Venous Thromboembolic Events

Overview of the Duration of Exposure in Orthopedic Studies in Venous Thromboembolism Prevention - Treated Subjects

	Apixaban 2.5 mg BID	Apixaban 5 mg BID	Apixaban 10 mg BID	Apixaban 5 mg QD	Apixaban 10 mg QD	Apixaban 20 mg QD	Enoxaparin 40 mg QD	Enoxaparin 30 mg Q12h	Warfarin
CV183035	N = 2673	--	--	--	--	--	N = 2659	--	--
Mean (SD), days Min, max	34.0 (7.68) (1.0, 46.0)	--	--	--	--	--	33.9 (7.79) (1.0, 60.0)	--	--
CV185047	N = 1501	--	--	--	--	--	N = 1508	--	--
Mean (SD), days Min, max	12.1 (3.14) (1.0, 67.0)	--	--	--	--	--	12.1 (2.75) (1.0, 41.0)	--	--
CV185034	N = 1596	--	--	--	--	--	--	N = 1588	--
Mean (SD), days Min, max	11.9 (9.55) (1.0, 380.0)	--	--	--	--	--	--	11.6 (2.53) (1.0, 16.0)	--
CV185010	N = 154	N = 153	N = 153	N = 151	N = 155	N = 151	--	N = 149	N = 151
Mean (SD), days Min, max	10.4 (2.61) (1.0, 16.0)	10.3 (2.46) (1.0, 15.0)	10.3 (2.62) (2.0, 14.0)	10.4 (2.62) (1.0, 15.0)	10.2 (2.58) (1.0, 14.0)	10.4 (2.50) (1.0, 16.0)	--	10.5 (2.37) (1.0, 15.0)	10.2 (2.37) (2.0, 15.0)

[11] Major bleeding was defined as a decrease in haemoglobin of 2g/dl or more during the treatment period, a transfusion of 2 or more units of packed red cells, bleeding into a critical site, eg intracranial haemorrhage or fatal. CRNM was defined as significant epistaxis, GI bleed, significant haematuria, significant haematoma, bruising or ecchymosis, or haemoptysis. Minor bleeding events were those that did not meet the above criteria. Fatal bleeding events were those defined by ICAC as the primary cause of death or contributed significantly to death.

Adverse events

There were no clinically relevant demographic differences between the apixaban 2.5 mg qd and enoxaparin treatment groups. Mean age was 61 years in the THR study and >65 years in the TKR studies with 12-19% in the very elderly age group (≥75 years). The main risk factor for DVT in all groups was previous lower limb orthopaedic surgery.

Bleeding

Bleeding event rates in the two studies using enoxaparin 40 mg qd as the comparator (CV185035 and CV185047) were similar during the treatment period in the apixaban and enoxaparin groups. The combined summary of bleeding endpoints is shown in Table 12. In 4174 subjects treated with apixaban 2.5 mg bd, major or CRNM bleeding occurred in 4.36% of subjects compared with 4.94% of 4167 subjects treated with enoxaparin 40 mg qd.

In the supportive Phase III study (CV185034), the incidence of major or CRNM bleeding in subjects who received apixaban 2.5 mg bd was significantly lower compared with those who received the higher comparator dose of enoxaparin 30 mg q12h (2.88% versus 4.28% respectively, p<0.035) (Table 13).

Table 12: Summary of bleeding endpoints – pooled CV185035 and CV185047

Apixaban
BMS-562247

Module 2.7.4 Summary of Clinical Safety
Prevention of Venous Thromboembolic Events

Summary of Bleeding Endpoints During the Treatment Period - Treated Subjects (Pooled CV185035 and CV185047)

	Apix 2.5mg BID N=4174	Enox 40mg QD N=4167
MAJOR BLEEDING, N	31	32
EVENT RATE (%)	0.74	0.77
95% CI FOR EVENT RATE	(0.52, 1.06)	(0.54, 1.09)
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-0.02	
95% CI FOR RISK DIFFERENCE	(-0.40, 0.35)	
TWO-SIDED P-VALUE	0.8551	
MAJOR OR CLINICALLY RELEVANT NON_MAJOR BLEEDING, N	182	206
EVENT RATE (%)	4.36	4.94
95% CI FOR EVENT RATE	(3.78, 5.03)	(4.33, 5.65)
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-0.58	
95% CI FOR RISK DIFFERENCE	(-1.49, 0.32)	
TWO-SIDED P-VALUE	0.2054	
ANY BLEEDING, N	417	460
EVENT RATE (%)	9.99	11.04
95% CI FOR EVENT RATE	(9.12, 10.94)	(10.12, 12.03)
ADJ. RISK DIFFERENCE (%) (APIX-ENOX)	-1.10	
95% CI FOR RISK DIFFERENCE	(-2.39, 0.19)	
TWO-SIDED P-VALUE	0.1142	

Includes events with onset from first dose of blinded study drug through 2 days after the last dose of blinded study drug
Program Source: /gbs/prod/clin/programs/cv/185/maa-vtep/sas/rpt/rt-bj-bleed-civ-v01.sas 29OCT2009: 9:57:55

Table 13: Summary of bleeding endpoints – CV185034

Apixaban
BMS-562247

Module 2.7.4 Summary of Clinical Safety
Prevention of Venous Thromboembolic Events

Summary of Bleeding Endpoints During the Treatment Period - Treated Subjects (CV185034)

	Apix 2.5 mg BID N=1596	Enox 30 mg Q12h N=1588
MAJOR BLEEDING, N	11	22
EVENT RATE (%)	0.69	1.39
95% CI	(0.37, 1.25)	(0.91, 2.11)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.81	
95% CI	(-1.49, -0.14)	
p-value	0.0533	
CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	35	47
EVENT RATE (%)	2.19	2.96
95% CI	(1.58, 3.05)	(2.23, 3.93)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-0.77	
95% CI	(-1.87, 0.33)	
p-value	0.1709	
MAJOR OR CLINICALLY RELEVANT NON-MAJOR BLEEDING, N	46	68
EVENT RATE (%)	2.88	4.28
95% CI	(2.16, 3.84)	(3.39, 5.41)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.46	
95% CI	(-2.75, -0.17)	
p-value	0.0338	
ANY BLEEDING, N	85	108
EVENT RATE (%)	5.33	6.80
95% CI	(4.33, 6.55)	(5.66, 8.16)
ADJ. DIFF OF EVENT RATES (APIX-ENOX) (%)	-1.52	
95% CI	(-3.18, 0.13)	
p-value	0.0816	

Adjusted difference of event rates takes into consideration type of surgery as a stratification factor

No fatal bleeding events occurred in any subject receiving apixaban 2.5 mg bd in any study.

In the pivotal studies CV185035 and CV185047 during the follow up period, the composite of major/CRNM bleeding occurred in 0.15% of subjects receiving apixaban and in 0.42% of subjects receiving enoxaparin. The frequency of surgical site bleeding was similar in the apixaban and enoxaparin groups (5.73% and 6.07% respectively).

Other adverse events

In the four pooled studies, the frequency of common AE (reported in >1% of either treatment group) was similar in both groups (apixaban 64% and enoxaparin 67%) (Table 14). In general the AE profile of apixaban given post-surgery was similar to that of enoxaparin 40 mg qd given pre-surgery. AEs reported in >5% of apixaban subjects were nausea, constipation, pyrexia, procedural pain, vomiting, oedema, hypotension and dizziness.

Table 14: Summary of adverse events in the four trials (CV185035, CV185047, CV185034, CV185010)

Apixaban
BMS-562247

Module 2.7.4 Summary of Clinical Safety
Prevention of Venous Thromboembolic Events

Summary of Adverse Events During the Treatment Period and Post-surgery Treatment Period - Treated Subjects (CV185035, CV185047, CV185034, and CV185010)

	CV185035		CV185047		CV185034		CV185010	
	Apix 2.5 mg BID (N=2673)	Enox 40 mg QD (N=2659)	Apix 2.5 mg BID (N=1501)	Enox 40 mg QD (N=1508)	Apix 2.5 mg BID (N=1596)	Enox 30 mg q12h (N=1588)	Apix 2.5 mg BID (N=154)	Enox 30 mg q12h (N=149)
Treatment Period								
Death, n (%)	3 (0.1)	2 (<0.1)	2 (0.1)	0	3 (0.2)	5 (0.3)	2 (1.3)	0
SAEs, n (%)	184 (6.9)	172 (6.5)	72 (4.8)	88 (5.8)	123 (7.7)	123 (7.7)	13 (8.4)	13 (8.7)
Discontinuations Due to AEs, n (%)	91 (3.4)	111 (4.2)	40 (2.7)	44 (2.9)	60 (3.8)	58 (3.7)	9 (5.8)	4 (2.7)
AEs, n (%)	1752 (65.5)	1811 68.1)	786 (52.4)	836 (55.4)	1149 (72.0)	1172 (73.8)	125 (81.2)	117 (78.5)
Post-surgery Treatment Period[a]								
Death, n (%)	3 (0.1)	1 (<0.1)	2 (0.1)	0	--	--	--	--
SAEs, n (%)	164 (6.1)	152 (5.7)	64 (4.3)	82 (5.4)	--	--	--	--
Discontinuations Due to AEs, n (%)	77 (2.9)	91 (3.4)	33 (2.2)	38 (2.5)	--	--	--	--
AEs, n (%)	1562 (58.4)	1607 (60.4)	681 (45.4)	729 (48.3)	--	--	--	--

[a] Events occurring during the Post-surgery Treatment Period are a subset of events occurring during the Treatment Period.

AEs of special interest

An increase in thrombotic events immediately following cessation of therapy has been described for heparin, warfarin and other thrombin inhibitors. Event rates for the composite of MI or stroke were similar in the treatment and follow up periods for both treatments in the two pooled studies using the enoxaparin 40 mg qd comparator. Four apixaban subjects experienced MI compared with one enoxaparin subject but all occurred at least two weeks after the cessation of randomised treatment.

A safety update relating to neurological events was submitted by the sponsor for inclusion in the submission. In the dose ranging study CV185010, one case of amyotrophic lateral sclerosis (ALS) was reported in the apixaban 10 mg qd group, and one case of Guillain-Barré Syndrome (GBS) was reported in the apixaban 5 mg qd group. Enhanced surveillance for neurological events in the Phase III program was implemented but no further cases were reported in the orthopaedic VTEp studies.

Serious adverse events and deaths

The frequency of deaths, SAE, AEs leading to discontinuation and non-serious AEs for the four VTEp studies is shown in Table 14. Death rates during the treatment period were comparable in the apixaban [10 (0.2%)] and enoxaparin [7 (0.1%)] treatment groups. During the follow up period, there were 3 deaths (0.05%) in apixaban subjects and 2 (0.03%) in subjects receiving enoxaparin.

In the four pooled studies, the SAE of PE with the outcome of death occurred in 5 (0.08%) subjects in the apixaban group and 1 (0.02%) in the enoxaparin group. In the pooled studies using the enoxaparin 40 mg qd comparator, there was one death ((<0.1%) in the apixaban group and none with enoxaparin.

Five subjects in the apixaban group and six subjects in the enoxaparin group had non-VTE related SAE with the outcome of death. One death was considered possibly related to

study treatment; the others were considered to be not, or unlikely to be related to study treatment.

In the four pooled studies in the treatment period, the frequency of SAEs was similar in the apixaban (6.6%) and enoxaparin (6.7%) treatment groups. In the pooled pivotal studies (CV185035 and CV185047), the incidence of SAEs was similar between treatment groups (6.1% of subjects receiving apixaban and 6.2% of subjects receiving enoxaparin). In the pooled four studies, the most common SAEs with onset during the treatment period were DVT and PE in either treatment group. No SAE was reported for >1% of subjects in either treatment group and most SAEs were reported for <0.1% of subjects.

Laboratory findings

Thrombocytopenia

In the pooled pivotal studies (CV185035 and CV185047), the incidence of adjudicated thrombocytopenia was slightly lower in the 4174 apixaban subjects (0.05%) compared with that in the 4167 enoxaparin subjects (0.12%).

Liver function

Three independent hepatologists provided blinded assessments of subjects with concurrent elevations of ALT > 3xULN and bilirubin >2xULN and/or pre-selected SAEs related to elevated LFTs. Most LFT elevations occurred in the immediate postoperative period and recovered quickly during the convalescent period.

LFT abnormalities were, in general, uncommon in both the treatment and follow up periods and similar in both treatment groups. Clinically significant LFT abnormalities tended to occur in the perioperative period with associated blood loss, hypotension, infection and multiple concomitant medications.

AEs related to LFT elevations were reported in 3.5% of subjects in the apixaban group and in 5.1% of the enoxaparin group. SAEs related to LFT elevation during the treatment period were reported in four (<0.1%) apixaban subjects and one (<0.1%) enoxaparin subject. AEs related to LFT elevations, during the treatment period and leading to discontinuation were reported for 7 (0.1%) subjects in each treatment group. All LFT abnormalities resolved after drug discontinuation with the exception of one subject who died of non-hepatic related events.

Marked laboratory abnormalities

There were no differences between apixaban and enoxaparin treatments in the frequencies of clinically significant laboratory abnormalities. In the four pooled VTEp studies, the most common marked abnormalities were low haemoglobin and haematocrit with a similar frequency in each treatment group.

Vital signs and ECG abnormalities

Vital signs (blood pressure and heart rate) and ECGs were recorded per protocol at the baseline visits. Subsequently, any clinically significant changes were recorded as an AE. The frequency of clinically significant changes was low (<1%) in each group in each of the four studies.

Safety in special populations

There were no obvious differences in safety outcomes between subgroups defined by age, gender, race, BMI and body weight, and the overall treatment population.

Safety related to drug-drug interactions and other interactions

Eleven apixaban drug interaction studies have been conducted. Ketoconazole (a strong CYP3A4 and P-gp inhibitor) had the largest effect on apixaban PK, with an approximately x2 increase in exposure. Naproxen, an inhibitor of P-gp, increased apixaban exposure by 50-60%, while rifampicin, a strong CYP and P-gp inducer, reduced apixaban exposure by approximately 40%.

Drugs with the potential to cause drug-drug interactions were either excluded or strongly discouraged in the four VTEp studies so their possible effects on safety have not been studied in the orthopaedic surgery setting.

Discontinuation due to Adverse Events

In the four pooled VTEp studies, the incidence of discontinuations due to AEs was similar in the apixaban (3.4%) and enoxaparin groups (3.7%). No AE leading to discontinuation was reported for >1% of subjects in either group. The most common AE leading to discontinuation in both groups were DVT and PE. DVT occurred in 0.3% of subjects receiving apixaban and 0.4% in subjects receiving enoxaparin. PE occurred in 0.4% of subjects receiving apixaban and in 0.2% of subjects receiving enoxaparin.

Non-supportive study: APPRAISE-2 (CV185068), in acute coronary syndrome

Bleeding

There was an excess of bleeding in the apixaban group (Treatment B) compared with placebo (Treatment A) (Table 15). The excess was approximately 2-3 times greater, depending on the assessment criteria employed (not discussed in this review) and new events continued throughout the treatment period. There were two intracranial haemorrhages in the placebo group and ten in the apixaban group, most occurring in subjects receiving mono- and dual anti-platelet therapy. There was one fatal bleed in the placebo group compared with five in the apixaban group.

Table 15: Bleeding events in APPRAISE-2

	Treatment A	Treatment B	Overall
Any Bleeding	239 / 3138 (7.6%)	549 / 3151 (17.4%)	788 / 6289 (12.5%)
Intracranial Bleed	2 / 3139 (<0.5%)	10 / 3153 (<0.5%)	12 / 6292 (<0.5%)
Gastrointestinal Bleeding	40 / 3138 (1.3%)	91 / 3151 (2.9%)	131 / 6289 (2.1%)
Fatal Bleed	1 / 3138 (<0.5%)	5 / 3151 (<0.5%)	6 / 6289 (<0.5%)
TIMI Bleeding (c)			
Major	15 / 3138 (<0.5%)	34 / 3151 (1.1%)	49 / 6289 (0.8%)
Minor	9 / 3138 (<0.5%)	27 / 3151 (0.9%)	36 / 6289 (0.6%)
Minimal	29 / 3138 (0.9%)	70 / 3151 (2.2%)	99 / 6289 (1.6%)
Indeterminate	186 / 3138 (5.9%)	413 / 3151 (13.1%)	599 / 6289 (9.5%)

	Treatment A	Treatment B	Overall
TIMI Major or Minor	24 / 3138 (0.8%)	61 / 3151 (1.9%)	85 / 6289 (1.4%)
ISTH Bleed (c)			
Major	33 / 3138 (1.1%)	71 / 3151 (2.3%)	104 / 6289 (1.7%)
Clinically Relevant Non-Major	40 / 3138 (1.3%)	101 / 3151 (3.2%)	141 / 6289 (2.2%)
Minor	166 / 3138 (5.3%)	372 / 3151 (11.8%)	538 / 6289 (8.6%)
GUSTO Bleeds (b)			
Severe	8 / 3138 (<0.5%)	37 / 3151 (1.2%)	45 / 6289 (0.7%)
Moderate	8 / 3138 (<0.5%)	15 / 3151 (<0.5%)	23 / 6289 (<0.5%)
Mild	219 / 3138 (7.0%)	496 / 3151 (15.7%)	715 / 6289 (11.4%)
Other	4 / 3138 (<0.5%)	1 / 3151 (<0.5%)	5 / 6289 (<0.5%)

Adverse events

Apixaban appeared to be well tolerated with a similar incidence of non-serious AEs in apixaban subjects (38.2%), compared with placebo (37.3%).

Serious adverse events and death

The incidence of SAEs (other than MI, unstable angina, cerebrovascular accident and bleeding) was approximately 15% in both treatment groups. There were ten more deaths in the apixaban group. Although a small treatment benefit based on the primary endpoint could not be excluded, mortality appeared to be higher in the apixaban group compared with placebo.

Laboratory abnormalities

The incidence of laboratory abnormalities was similar in both groups. Specifically, the frequency of significant LFT abnormalities was similar in subjects on apixaban compared with placebo.

Comment

The study was stopped because the increased risk of bleeding was unacceptably high in subjects who received apixaban 5 mg bd when compared to placebo. More than 80% of patients received dual antiplatelet therapy in this study and similar studies of warfarin and dual antiplatelet therapy have also shown an excess of bleeding. The gain in efficacy by adding apixaban to antiplatelet therapy was likely to be no better than 6% when compared to placebo. This benefit would be of little clinical significance and would not

offset a significant risk of non-fatal and fatal bleeding events in patients receiving apixaban.

Evaluator's overall conclusions on clinical safety

In general, the safety profile of apixaban 2.5 mg bd was similar to that of enoxaparin 40 mg qd in four VTEp studies in subjects undergoing TKR and THR. No specific safety signals were detected.

The stated objective of the clinical program was similar or less frequent bleeding with apixaban compared with enoxaparin and this has been realised. Bleeding is the most serious potential consequence in subjects receiving anticoagulation for orthopaedic surgery. There were no deaths related to bleeding in any subject who received apixaban. The frequency of bleeding events of all severity was similar in both groups when the comparator was enoxaparin 40 mg qd (given before surgery) and numerically lower in favour of apixaban in studies with enoxaparin 30 mg q12h (given after surgery).

In the Phase II dose ranging study, the frequency of bleeding increased with increasing doses of apixaban. However, at all doses the risk of life threatening bleeding was relatively low. PK and PD variability is small and predictable so the potential risk for bleeding with the concomitant use of CYP and P-gp inhibitors is measurable but low. The same may also be true following accidental or deliberate drug overdose.

Analysis of small subject numbers in various subgroups, including the elderly, those with mild renal impairment and extremes of BMI suggested no increased risk compared with the larger study population.

The frequencies of SAEs, AEs and AEs leading to discontinuation during the treatment period were similar in the apixaban and enoxaparin groups. The most common events (gastrointestinal, pain, fever, hypotension, anaemia) were those expected in the post-surgical setting.

DVT and PE were the most common SAEs in the four pooled studies. The frequency of DVT was similar in each group but the frequency of PE was numerically higher in the apixaban group. However, this is likely to be a chance finding as the frequency of both DVT and PE was similar in both treatment groups in the two pooled studies using enoxaparin 40 mg qd as the comparator.

There was no evidence of a rebound hypercoagulation syndrome. VTE events were infrequent in the post-treatment observation treatment and the frequency of MI and stroke was very low. Thrombocytopenia was infrequent in both groups.

Most LFT abnormalities occurred in the immediate post-operative setting with blood loss, sepsis, anaesthetics, hypotension, concurrent illness and concomitant medications as potentially confounding factors. The frequency was relatively low and most resolved rapidly in the post-operative period. There was no placebo control but LFT abnormalities were numerically less frequent with apixaban than with enoxaparin, a medication without specific hepatic safety concerns. Idiosyncratic or hepatotoxic drug induced liver injury is inevitably difficult to detect in an acute surgical setting. However ongoing studies in >19,000 subjects in other studies have revealed no signals to date.

GBS is known to occur after infections, vaccinations and surgery and appears to be more frequent in patients who have acute medical conditions. Comparison between incidence rates in the general population and study populations including surgery and acute medical conditions is difficult. Thus, it is currently not possible to exclude the likelihood that the numerical excess of GBS cases are related to such confounding factors in the trial subjects.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

Has the bioequivalence of the commercial tablet and the clinical trial tablet been established by an *in vivo* study rather than by dissolution rates of the tablets alone?

Some further clarification of the dependence of apixaban PK on genetic polymorphisms would be of interest. Samples for this analysis were collected in the studies but no data was presented.

Pharmacodynamics

Are there any studies of potential genetic factors which might explain the PD variability in response to apixaban?

Safety

Why was an additional arm, enoxaparin 40 mg qd not included in the dose ranging study CV185010?

Can guidance based on clinical trial data be provided for when anti-platelet agents or low dose aspirin should be stopped before elective surgery, and restarted afterwards?

Sponsor response

A justification for not performing a study to assess the bioequivalence of the commercial tablet and the clinical trial tablet was accepted by the quality evaluator.

There is little potential for a genetic polymorphism to have a clinically significant impact on apixaban exposure because apixaban is eliminated by multiple pathways, including both renal and non-renal routes, which mitigates the impact of a genetic polymorphism in one elimination pathway. Furthermore, a favourable apixaban safety and efficacy profile has been established in a population that is likely to include a high proportion of CYP3A5 poor metabolisers. Genetic variability in apixaban pharmacokinetics is also unlikely to be a contributing factor in the observed variability in response to the mPT, INR and aPTT clotting tests, which is most likely attributed to the nature of the assays.

The choice of comparator for the dose ranging study was mainly due the 40 mg qd regimen of enoxaparin not being approved for patients undergoing TKR in the United States and Canada, where the majority of subjects were randomised.

A decision on when to cease and restart antiplatelet agents or low dose aspirin is based on physician judgment, taking into consideration the ongoing risk for bleeding together with the risk of thrombosis for the individual patient.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

Apixaban PK are linear and exposure to apixaban increases proportionally following oral administration of doses up to and including 10 mg bd. Apixaban absolute oral bioavailability is ~50%, and is not affected by administration with food. Apixaban reaches steady state concentrations after 3 days of dosing, consistent with the $t_{½}$ of approximately 12 hours and twice daily dosing.

Apixaban has low clearance and multiple routes of elimination. Apixaban does not have any unique human metabolites with relevant pharmacologic activity.

Apixaban does not require dose modification or dose restrictions for the following factors:

- age,
- gender,
- body weight related (generally less than 30% change in apixaban PK),
- race (White, Black/African American, Asian) (modest effects on apixaban PK),
- mild to severe renal impairment* (< 50% increase in apixaban exposure compared to normal renal function),
- mild to moderate hepatic impairment (no discernible effect on apixaban PK or PD),
- coadministration of strong inhibitors of both CYP3A4 and P-gp (~ 2-fold increase in apixaban exposure after administration with ketoconazole),
- coadministration of strong inducers of both CYP3A4 and P-gp* (~ 50% decrease in apixaban exposure after administration with rifampin).

The potential for apixaban to affect the PK of concomitantly administered medications is low.

* Apixaban is contraindicated in patients with severe renal impairment with a creatinine clearance < 15 mL/min and in patients receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp.

Pharmacodynamics

Apixaban is a potent, direct, reversible inhibitor of coagulation factor Xa. Anti-FXa activity exhibits a close, direct, linear relationship with apixaban plasma concentration. Steady state peak and trough anti-FXa activity with apixaban 2.5 mg bd dosing are expected to be 1.3 IU/mL (5th /95th percentile 0.67-2.4 IU/mL) and 0.84 IU/mL (5th /95th percentile 0.37-1.8 IU/mL), respectively, in subjects that receive apixaban for VTE following TKR or THR surgery.

Apixaban prolongs clotting time measurements such as INR, prothrombin time, and activated partial thromboplastin time. Following administration of 2.5 mg bd, changes in clotting time measurements are small and variable. Apixaban does not exhibit any secondary or off-target pharmacologic effects, including an effect on the QTc interval.

Clinical efficacy

Clinical efficacy was assessed in four VTEp studies conducted in 11,828 subjects. One study was conducted in THR and three in TKR. The risk of VTE is maximal at approximately two weeks after TKR and 4-5 weeks after THR, requiring more prolonged VTE prophylaxis following THR. However, the underlying pathophysiology and response to prophylaxis are otherwise similar and it is justifiable to include both operations in the one indication.

The pivotal Phase III studies were robust, large, randomised, double blind, double dummy, multicentre, multinational studies conducted according to full ICH GCP guidelines. The primary efficacy endpoint was determined by mandatory ascending, contrast venography, the gold standard investigation for DVT. A missing or non-evaluable rate of 30% was expected from similar studies so this was assumed a priori in the statistical plan. To minimise investigator bias, an experienced central adjudicating committee assessed all endpoints in all studies. The subjects, investigators and adjudicating committee were all blind to the randomised treatments which were appropriately double blinded.

The primary endpoint for clinical efficacy in the study program was defined as the composite of all VTE/all cause death. Asymptomatic distal or proximal DVT was detected

by mandatory ascending contrast venography at the end of the treatment period. Up to 30% of venograms are not performed for one reason or another in published VTEp studies. For this reason there was a pre-specified sensitivity analysis for missing venograms. In the four VTEp studies, missing or non-evaluable venograms were ≤30%, they were similar in both treatment groups and they did not affect the primary conclusions of the pivotal studies or the supportive study CV185034. CV185010 was a Phase II dose ranging study in TKR comparing warfarin, enoxaparin 30 mg q12h SC (the US approved dose regimen) and varying doses of oral apixaban given either qd or bd. The study demonstrated a clear dose response relationship for both efficacy (VTE prevention) and safety (clinically significant bleeding). It is unclear why a comparator dose of enoxaparin 40 mg qd was not included in addition to or instead of the warfarin arm. Nonetheless, the apixaban dose of 2.5 mg bd was clearly the most appropriate to be carried into the Phase III program. Apixaban 2.5 mg bd offered numerically similar or improved efficacy compared with enoxaparin with similar or improved safety.

In the pivotal Phase III study CV185047 in TKR, event rates for the primary endpoint were 14.88% (95% CI 12.71-17.36) in evaluable apixaban subjects, and 24.76% (95% CI 22.07-27.66) in subjects who received enoxaparin. The relative risk in favour of apixaban was 0.60 (95% CI 0.50-0.73; p<0.0001). For the secondary endpoint of major VTE, event rates were 1.09% (95% CI 0.62-1.88) in evaluable apixaban subjects and 2.17% (95% CI 1.47-3.18) in subjects who received enoxaparin. The relative risk in favour of apixaban was 0.50 (95% CI 0.26-0.97; p<0.0003).

In the pivotal study Phase III study CV185035 in THR, event rates for the primary endpoint were 1.30% (95% CI 0.87-1.94) in evaluable apixaban subjects, and 3.72% (95% CI 2.94-4.70) in subjects who received enoxaparin. The relative risk in favour of apixaban was 0.35 (95% CI 0.20-0.54; p<0.0001). Apixaban 2.5 mg bd was also superior to enoxaparin for the prevention of the composite endpoint of proximal DVT, non-fatal PE and VTE related death. Event rates were 0.45% (95% CI 0.24-0.85) in apixaban subjects, and 1.14% (95% CI 0.77-1.69) in subjects who received enoxaparin. The relative risk in favour of apixaban was 0.40 (95% CI 0.15-0.80; p<0.0001).

In the supportive Phase III study CV185034 in TKR, apixaban 2.5 mg bd had similar efficacy to enoxaparin 30 mg q12h although the pre-specified NI criterion was not met.

Efficacy in subgroups defined by age, gender, weight, BMI, renal function or ethnicity was similar to the overall treatment population although the numbers were too low to test statistical significance.

Demographics and baseline characteristics were similar and representative of the target population for apixaban. Exposure was similar between treatments. Discontinuations and withdrawal rates for AEs were acceptably low and similar in both treatment groups.

Treatment periods were 2 weeks for TKR and 5 weeks for THR and event rates were lower in THR. However, the relative risk reductions in favour of apixaban were similar in magnitude in both studies.

The evidence supporting increased efficacy in favour of apixaban is convincing.

Clinical safety

Bleeding event rates were similar with apixaban 2.5 mg bd compared with enoxaparin 40 mg qd and fewer compared with enoxaparin 30 mg q12h. There were no fatal bleeding events in any subject given apixaban.

In CV185047 in TKR, major bleeding occurred in 0.6% (95% CI 0.30-1.16) of 1501 apixaban subjects and 0.93% (95% CI 0.54-1.57) of enoxaparin subjects (not significant

[NS]). Major or clinically relevant non-major bleeding occurred in 3.53% (95% CI 2.71-4.60) of apixaban subjects and 4.77% (95% CI 3.81-5.98) of enoxaparin subjects.

In CV185035 in THR, major bleeding occurred in 0.82% (95% CI 0.54-1.25) of apixaban subjects and 0.68% (95% CI 0.42-1.08) of enoxaparin subjects (NS). Major or clinically relevant non-major bleeding occurred in 4.83% (95% CI 4.08-5.72) of 2673 apixaban subjects and 5.04% (95% CI 4.27-5.94) of enoxaparin subjects.

LFT and other laboratory abnormalities were comparable between groups or lower in subjects treated with apixaban, with no evidence of drug induced liver injury or other toxicities in either group. There was no placebo control and safety monitoring was confounded by the operative setting with associated blood loss, infection and concomitant medications. However, LFT abnormalities with apixaban were similar or less frequent than with enoxaparin which has no specific hepatic safety concerns despite wide usage worldwide. Reliance must be placed on good study design and conduct and LFT data from other completed and ongoing studies should be monitored to detect possible masked safety signals.

There was no evidence of a post-treatment increased coagulation 'rebound' phenomenon. The frequency of VTE events was low in the post-treatment follow up period. There were few arterial thrombotic events such as MI or stroke and severe thrombocytopenia occurred in only one subject.

There is a close exposure response relationship for all dose levels of apixaban up to 50 mg daily. Increased exposure will change the benefit risk ratio in favour of efficacy at the expense of increased risk of bleeding. The risk of bleeding identified in the dose ranging study appeared to be higher in subjects given apixaban 5 mg bd when compared with apixaban 2.5 mg bd. However, this was balanced by the reduced risk of VTE with apixaban 5 mg bd when compare with apixaban 2.5 mg bd.

There is little or no relevance of the APPRAISE-2 (CV185068) study to the VTE prevention submission. More than 80% of patients in that study received acute coronary syndrome antiplatelet therapy. Antiplatelet agents are contraindicated in elective THR and TKR surgery and patients receiving them were specifically excluded in the pivotal and supportive VTEp studies. Moreover, the dose of apixaban in CV185068 was 5 mg bd, a dose shown to carry an increased risk of bleeding when compared to apixaban 2.5 mg bd in the dose ranging study CV185010, and a twofold higher dose than that used in the VTEp studies. In addition, exposure in the VTEp studies was only 2-5 weeks, much less than that in CV185068. The incidence of fatal and non-fatal bleeding events was unacceptably high in CV185068 but no fatal or intracranial haemorrhage bleeding events occurred in the apixaban group in any of the VTEp studies when the dose was 2.5 mg bd. Moreover, more than half of the major bleeding events in the VTEp studies occurred immediately post-surgery and before the first dose of apixaban was given.

Efficacy endpoints cannot be compared because the primary endpoint in CV185068 was arteriothrombotic rather than venous thrombotic prophylaxis. Safety endpoints (other than MI, UA, CVA and bleeding) are also not strictly comparable because CV185068 was placebo controlled while the VTEp studies had active control. However, it is reassuring to note that the incidence of AE, non-fatal SAE and laboratory abnormalities was similar to placebo in subjects who received long-term treatment with apixaban 5 mg bd.

The results from APPRAISE-2 do not alter the conclusions or the balance of risk and benefit in the VTEp studies. A strengthening of the cautionary statement in the PI regarding concomitant antithrombotic agents is indicated and this has already been submitted by the applicant.

The cases of GBS are noteworthy but all had known risk factors for the syndrome. A direct causal relationship cannot be excluded but the incidence is low and it does not change the risk/benefit equation. Nonetheless, ongoing enhanced surveillance should be a mandatory precaution.

Benefit risk assessment

Benefits

From a PK point of view a benefit of apixaban may be its half-life of elimination of 12 hours. The drug is thus relatively quickly cleared from the system in cases of overdose for example. The lack of pharmacologically active metabolites may also be seen as an advantage since the actions are attributable to only the parent moiety. The main inactive metabolite has also been characterised kinetically and is generally well described in the studies presented.

Lower limb orthopaedic surgery carries an unacceptable risk of VTE and prevention trials with warfarin, heparin, LMWH and other agents have shown consistent benefit compared with placebo or no treatment. Enoxaparin has been widely studied and is currently the accepted gold standard for VTEp. However, enoxaparin must be given SC and orally effective agents such as apixaban offer an advantage if safety and efficacy are equivalent or superior.

Distal DVT in TKR and THR is the most commonly occurring event, captured in the composite endpoint of VTE and all cause death. DVT may cause significant local morbidity and discomfort which may become chronic. However, the sensitivity of DVT as a predictor of non-fatal and fatal PE can be questioned. Proximal DVT is the most commonly occurring event captured in the composite of major VTE (proximal DVT, non-fatal PE and VTE related death). In contrast to distal DVT, the importance of proximal DVT as a predictor of fatal and non-fatal PE is widely accepted, in particular in the current EMA guidance.

The two pivotal Phase III studies, CV185035 and CV185047, in THR and TKR respectively, demonstrated clinically meaningful RRR in favour of apixaban 2.5 mg bd compared with enoxaparin 40 mg qd which were highly statistically significant for the primary endpoint. More importantly, similar risk reductions were also apparent for the secondary efficacy endpoint of major VTE events.

The individual events of fatal and non-fatal PE occurred infrequently with both treatments with no apparent benefit in favour of apixaban. This apparent lack of benefit may be real, or may have happened by chance because event numbers were low. However, on balance there is little doubt that apixaban 2.5 mg bd is significantly more effective than enoxaparin 40 mg qd, with RRR 38-64% for both VTE and major VTE endpoints.

The supportive study CV185034 compared apixaban 2.5 mg bd with enoxaparin 30 mg q12h, a 50% larger comparator daily dose. There was RR of 1.02 in favour of enoxaparin and the NI criteria were not met. However, this difference is unlikely to be clinically meaningful.

Analyses in the overall study populations were compared with those in pre-determined subgroups defined by age, gender, race, body weight, BMI, renal function and geographical region. The numbers were small but the responses in each subgroup were similar to the general population.

Risks

Increased bleeding is a risk in the use of this drug. Response to the drug appears to be quite variable based on the parameters investigated (mPT, INR, PTT) in the PD studies.

Whether genetic factors underline this variability is not clear and has not been investigated by the sponsor.

Bleeding is the major concern for clinicians who are convinced of the benefits of VTE prophylaxis. The objective of the study program was similar or improved safety with apixaban 2.5 mg bd compared with enoxaparin 40 mg qd.

Bleeding event rates were indeed similar with apixaban 2.5 mg bd and enoxaparin 40 mg qd. No deaths due to bleeding occurred in apixaban subjects and major bleeding was <1% in both groups. CRNM was more common but similar with each treatment.

There were few deaths. AEs and SAEs were comparable between treatments and discontinuations due to AEs were approximately 3-4% in both groups. Interpretation of adverse events is difficult in the operative setting and reliance must be placed on good study design. The studies were all adequately blinded and randomised and treatment exposure and withdrawals were similar in each group.

Bleeding is the major risk associated with antithrombotic therapy. Bleeding events were closely monitored by the investigators during the inpatient period and by patient diary card post-discharge. All clinically significant bleeding was adjudicated by the central adjudicating committee to eliminate investigator bias. The studies were double blind, double dummy and randomised to further eliminate investigator and subject bias. Bleeding event rates were similar in TKR and THR despite the longer treatment duration for THR. Bleeding events of all severity were similar between treatment groups and bleeding event rates in subgroups appeared similar to the overall treatment population.

There was no evidence of hepatotoxicity and LFT abnormalities were similar or lower than enoxaparin. ALT >3xULN with bilirubin >2xULN was reported in <0.1% subjects.

The frequencies of death, SAEs, AEs and withdrawals due to AEs were similar in both treatment groups.

There was no evidence of rebound hypercoagulation after treatment was stopped in either TKR or THR and events in the follow up period were in general low. Arteriothrombotic events such as MI and stroke were few.

The perioperative setting is associated with numerous compounding variables including blood loss, infection, hypotension and concomitant medications. Assessment of drug toxicity in orthopaedic studies cannot be optimal but there were no differences or trends between apixaban and enoxaparin regimens. Data from over 19,000 subjects in ongoing medical prophylaxis studies will offer long term hepatotoxicity and safety data in more controlled circumstances.

The strongest inhibitors of CYP3A4 and/or P-gp have the potential to double apixaban exposure. Smaller increases in exposure of up to 25% may also be expected in older subjects, females, subjects with low body weight, and subjects with impaired renal function. Oral bioavailability is 50%, approximately linear at lower doses and predictable with modest intra- and inter-subject variability. Peak and trough fluctuations with bd dosing of up to 1.6 may also be expected.

Fluctuations in this range alter the risk profile and caution should be observed. However, life threatening or fatal VTE or bleeding events are unusual and the potential for doubling exposure in subject groups described above does not warrant dose modification.

The same arguments suggest that clinical monitoring of FXa activity is not required. Traditional testing, using INR and PT, is unreliable and would not be helpful in most clinical settings. Major bleeding may occur with normal or high drug exposure and should be managed conservatively as described in the proposed Product Information. There is no

specific antidote in the event of accidental or deliberate overdose. However, apixaban has a half life of approximately 12 hours and blood levels are likely to fall to sub-therapeutic levels within 24-48 hours.

Balance

There is universal agreement supporting the use of antithrombotics for VTE prevention in lower limb orthopaedic surgery and other indications.

Without prophylaxis, THR or TKR are both associated with a high risk of VTE. The ACCP guidelines for VTEp state that distal DVT, proximal DVT, clinically apparent PE and fatal PE occur in 40-80%, 10-20%, 4-10% and 0.2-5% of patients respectively.[10] Distal or proximal DVT is associated with short and long term morbidity including post-thrombotic syndrome (PTS).[12] The symptoms of PTS include dependent swelling, pain, oedema, venous ectasia, skin induration and intractable venous leg ulcers. This may lead to reduced mobility and increased requirements for medical and nursing care, particularly in elderly patients. Pulmonary embolism may be asymptomatic or result in dyspnoea, hypoxia, hypotension, heart failure, circulatory collapse and death.

Prophylactic antithrombotic therapy has proved highly effective in lower limb surgery but it is limited by a significant risk of bleeding.

Enoxaparin is the most widely studied LMWH and it has replaced heparin and warfarin as the gold standard for VTE prophylaxis. However, it must be given SC, it causes injection site reactions, at a dose of 40 mg qd it is given before surgery and there is a small risk of clinically significant thrombocytopenia. Novel oral thrombin inhibitors such as dabigatran and melagatran have proved effective, although ximelagatran has unacceptable hepatotoxicity. Oral Factor Xa inhibitors, such as fondaparinux and rivaroxaban have also proved effective.

The objective of the clinical program was to select an effective dose for apixaban offering similar or improved safety compared with the gold standard LMWH enoxaparin and this was achieved. Apixaban 2.5 mg bd caused no bleeding related deaths and the frequency of other bleeding events was comparable. The risks of bleeding cannot be discounted but the risks of a life threatening bleeding event with current drug regimens are low and have been widely accepted in the medical community. There was no evidence of any drug toxicity so the evidence clearly favours no additional risk for apixaban compared with enoxaparin.

The efficacy benefit of apixaban compared with that of enoxaparin is approximately two-fold. Most numerical benefit relates to a reduction in distal DVT. However, although events were less frequent, major VTE events were significantly lower with apixaban. There was no benefit for non-fatal and fatal PE but events were few and much lower than would be expected in an untreated population.

Bleeding is an inevitable risk of antithrombotic VTE agents. However, there were no bleeding related deaths in subjects who received apixaban. Major bleeding events were also few (<1.0%), mostly related to wound bleeding and often managed without discontinuation of the study drug. Other safety parameters were generally similar with no evidence of hepatotoxicity.

There is universal appreciation of the benefits of VTE prophylaxis in lower limb surgery. Apixaban offers significantly improved efficacy compared with enoxaparin, the current

[12] Ashrani AA, Heit JA. Incidence and cost of post-thrombotic syndrome: J Thromb Thrombolysis 2009; 28: 465-476.

gold standard for VTE prophylaxis, without additional risk of bleeding or other adverse events. Another benefit of apixaban is that it is administered orally.

Conclusions

The overall benefit risk balance of apixaban is positive. It was recommended that apixaban 2.5 mg bd be approved for the proposed indication of

Prevention of venous thromboembolic events in adult patients who have undergone elective total hip or total knee replacement surgery.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The summary of the ongoing safety concerns as specified by the sponsor was as follows:

Important identified risk:

- Bleeding

Potential risks:

- Transient liver function test (LFT) abnormalities

Missing information:

- Paediatrics
- Pregnant/lactating women
- Severe hepatic impairment
- Severe renal impairment
- Hip fracture surgery or other non-elective orthopaedic procedures (off-label use)

The clinical aspects of the Safety Specification were reviewed by the clinical evaluator. The evaluator noted that no specific safety signals were detected in subgroups in the VTE prevention studies. However, additional data in very elderly subjects and those with moderate to severe renal failure or hepatobiliary disease would be valuable. Data in non-elective, emergency lower limb surgery would also be valuable. The safety specifications detailed in the Risk Management Plan are consistent with the AE profile as demonstrated in the clinical trials. In addition to routine pharmacovigilance, events of special interest will be closely monitored, LFT abnormalities in particular.

The nonclinical aspects of the Safety Specification were reviewed by the nonclinical evaluator and were found to be generally consistent with the nonclinical data. The reviewer noted a number of areas which required clarification.

The OPR reviewer made the following recommendations:

- The relevant sections of the RMP pertaining to the risk of bleeding and of pharmacodynamic drug interactions should be updated regarding the safety related issues leading to the termination of the APPRAISE-2 study and the discontinuation of the high dose arms of the APPRAISE-1 study (a dose ranging study in patients with ACS), or the sponsor should provide justification why not to include this.

- Given that drugs with the potential to cause drug-drug interactions (both pharmacokinetic and pharmacodynamic) were either excluded or strongly discouraged in the four VTE prevention studies, their possible effects on safety have not been adequately studied in the orthopaedic surgery setting. Data from the APPRAISE-1 and -2 trials indicate a more pronounced pharmacodynamic effect (bleeding) with the concomitant use of antiplatelet drugs. Therefore it was recommended that the sponsor should include drug-drug interactions in the RMP safety specifications as important limited/missing information, or the sponsor should provide justification why not to include this.
- Neurological safety should be included in the RMP as important limited/ missing information, or adequate justification provided for this not being included.
- The toxicology evaluator has identified that apixaban was likely to be secreted in human breast milk and is an important point to be considered in evaluating the RMP. Exposure to apixaban could increase the risk of bleeding in breastfed infants. Infants with apixaban related bleeding would have normal coagulation tests, which would hinder identification of the cause and management of the adverse event. It was suggested that the sponsor be asked to further consider the clinical consequences of breastfeeding by women receiving apixaban (for example, by calculating the likely exposure of a breastfed infant to apixaban) to support appropriate risk minimisation strategies for this risk (such as a strengthened warning of risk in the PI).
- While it was noted that the inclusion criteria for most of the apixaban studies do not have upper age restrictions, there is less data available on elderly subjects (≥ 75 years). Approximately 16% of subjects ≥ 75 years were exposed to apixaban in the 4 VTE prevention studies (CV185010, CV185034, CV185035 and CV185047). In the clinical setting this population of patients are more likely to have concomitant diseases, be taking other medications with the potential for drug-drug interactions, have reduced hepatic and renal function and be at higher risk of falls and post-operative complications, including bleeding. It was therefore recommended that the use of apixaban in patients ≥ 75 years be included in the RMP as an ongoing safety concern based on limited/missing information, or the sponsor should provide justification why not to include this.
- There is limited experience of the effects and treatment of apixaban overdose, particularly with respect to laboratory (coagulation profile) monitoring and the management of severe bleeding. It was recommended that management of overdose and excessive haemorrhage be included in the RMP as an ongoing safety concern based on limited/missing information, or the sponsor should provide justification why not to include this.

Pharmacovigilance Plan

The sponsor proposed routine pharmacovigilance (PhV) for all the ongoing safety concerns.[13] The following additional PhV actions were proposed by the sponsor:

[13] Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Important identified risk: bleeding

- Additional information from ongoing and future clinical trials.
- External blinded adjudication of bleeding events in pivotal clinical trials.
- Frequent aggregate reviews on Events of Special Interest (clinical trials and post-market).
- Additional PhV by evaluation of a drug utilisation study.

Important potential risk: transient liver function test abnormalities

- Additional information from ongoing and future clinical trials. Specific algorithms used for monitoring LFTs in the clinical trials were provided by the sponsor.
- Expedited follow up of selected liver cases and supplemental case report forms to obtain more detailed information and assessment in clinical studies regarding liver events of interest (for example, hepatitis, liver failure, jaundice and/or ALT 3xULN and total bilirubin 2xULN).
- External blinded hepatologist panel assessment for targeted hepatic events from ongoing and future clinical trials.
- Targeted questions for postmarket spontaneous reports of liver events. For specific cases of severe liver events (for example, fulminant hepatitis, liver failure, hepatic encephalopathy), based on medical judgement, an *ad hoc* follow up with the reporter will be performed as needed.
- Frequent aggregate reviews on events of special interest (clinical trials and post-market).
- Additional PhV by evaluation of a drug utilisation study.

Important missing information: paediatric patients

- A paediatric development program is planned including trials of apixaban in children with an indwelling central venous catheter and the prevention of thromboembolic disease in children with cardiac disease. The paediatric programme has been deferred pending the demonstration of the safety and efficacy in prevention of adult VTE's.

Important missing information: pregnant/lactating women

- Pregnancy outcome follow up of spontaneous reports.

Important missing information: severe hepatic impairment

- Additional information from regular postmarket surveillance.

Important missing information: severe renal impairment

- Additional information from ongoing clinical trials.

Important missing information: off- label use

- Assessment of the potential for off-label use by evaluation of a drug utilisation study.

The OPR reviewer made a number of recommendations regarding these PhV activities.

Risk Management Activities

The sponsor concluded that routine risk minimisation was sufficient to monitor any emerging safety signal and manage potential risks.[14] The OPR reviewer recommended a

[14] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

number of changes to the proposed PI to manage these risks but this discussion is beyond the scope of this AusPAR.

Sponsor Response

The sponsor agreed to continue to monitor for Guillain-Barré Syndrome (GBS) and amyotrophic lateral sclerosis (ALS) and to provide cumulative reviews of these events in PSURs; however they did not accept the recommendations for enhanced pharmacovigilance. While the data provided by the sponsor was reassuring advice from the Advisory Committee on the Safety of Medicines (ACSOM) and the recommendation in the clinical evaluation report were that there should be ongoing enhanced surveillance. As such it was recommended that the sponsor implements enhanced pharmacovigilance of all GBS adverse events in the post-market setting.

It had been recommended that the following safety concerns be added to the RMP as limited/missing information:

- Drug-drug interactions.
- Serious neurological events.
- Elderly patients >75 years.
- Overdose / coagulation profile monitoring / management of severe bleeding.

The sponsor agreed to include overdose/coagulation profile monitoring/management of severe bleeding as limited/missing information in the RMP. Routine pharmacovigilance activities and risk minimisation was proposed. The sponsor did not agree to the other safety concerns being added to the RMP. The sponsor stated that drug-drug interactions have been adequately addressed in the interaction studies. Regarding serious neurological events, the sponsor did not propose to list potentially rare events as limited or missing information. The sponsor stated that apixaban has been adequately studied in the very elderly population in the Phase II/III orthopaedic VTE prevention clinical trials (12% of subjects were > 75 years in the THR study and >19% in the TKR studies).

The OPR reviewer noted that the exclusion of drug-drug interactions is acceptable if the sponsor implements the proposed enhanced monitoring of post-market reports of bleeding events and includes a cumulative review of suspected drug-drug interaction ADRs in the Periodic safety Update Report (PSUR).

While rare, serious neurological events (particularly GBS) should be included in the RMP as a potential safety concern because GBS has been identified as a possible safety signal that requires further monitoring and characterisation in the postmarket period.

There has been only limited exposure to the very elderly in the apixaban VTE prevention trials. Because of the clinical trial exclusion criteria, this population may not have been representative of very elderly patients in the normal clinical setting. The clinical evaluator also noted that data in very elderly patients would be valuable. It was therefore recommended that apixaban use in elderly patients > 75 years be included in the RMP ongoing safety concerns as limited/missing information. Routine pharmacovigilance would be acceptable at this stage.

In the context of an apparent increased risk of bleeding, possibly related to factors that increase apixaban exposure (for example, dose; age > 65 years; CrCI < 60 mL/min) and/or potentiate the pharmacodynamic effects of apixaban (for example, concomitant antiplatelet treatment), the OPR reviewer had recommended that the sponsor conduct a postmarket pharmacoepidemiological safety study that is scientifically valid, well designed and suitably powered. A prospective cohort design was preferable. The sponsor rejected this postmarketing safety study recommendation on the basis of a lack of evidence of increased bleeding risk with apixaban compared to the comparator in the VTE

prevention trials, even with concomitant administration of NSAIDs or other medications with anti-platelet or anticoagulant activity after surgery or factors which may increase apixaban exposure such as age (>65yrs) or CrCl<60 mL/min. The sponsor also identified potential difficulties with sub-group analysis in the study design.

The OPR reviewer accepted that there was no increase in bleeding event rates for apixaban compared to the enoxaparin comparator in the VTE prevention trials and that no fatal bleeding events occurred in any subject receiving apixaban 2.5 mg bd. Furthermore, the conclusion in the clinical evaluation of the APPRAISE-2 data was that the study bore little or no relevance to the VTE prevention submission. However the concern raised by the OPR reviewer about serious bleeding risk was with respect to how the findings from APPRAISE-1 and APPRAISE-2 might suggest a risk in the broader clinical patient population. On balance, it was accepted that a specific postmarketing study is not required on the basis of the current evidence, however it was recommended that enhanced pharmacovigilance for bleeding events be implemented by the sponsor. The sponsor outlined a proposal to commit to targeted questions for spontaneous reports of bleeding via the use of standardised queries supplemented by specific inquiry about the bleeding characteristics and history of hepatic or renal impairment. This was acceptable in principle with some recommended variations.

There were also a number of issues concerning the proposed PI and Consumer Medicines Information (CMI) document but these are beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator recommended approval with respect to chemistry and quality control. In relation to bioavailability, it was noted that the absolute bioavailability was 50% and that food had no effect on apixaban pharmacokinetics. PSC also considered this submission and had no objections on pharmaceutic or biopharmaceutic grounds.

Nonclinical

The nonclinical evaluator had no objections to the registration of apixaban for the proposed indication. The data package was comprehensive and adequate to support the proposed use in clinical practice. Apixaban produced a prolonged prothrombin time in rats but negligible change in rabbits and dogs. Secondary and safety pharmacology studies did not raise significant concerns. Apixaban is eliminated by multiple pathways including metabolism, renal and biliary excretion. It does not inhibit or induce CYP450 enzymes but CYP3A4 is the major enzyme responsible for its metabolism. It is a substrate for P-gp and BCRP transporters (apical membrane of intestinal epithelial cells and liver canalicular membranes), thus strong inhibitors or inducers of these pathways of elimination may alter plasma concentrations. A P-gp study using digoxin did not detect significant P-gp inhibitory activity by apixaban. Toxicity studies in animals showed prolongation of plasma coagulation parameters, injection site haemorrhage, decreased potassium, increased sodium and chloride (electrolyte changes not always dose dependent and did not worsen with long term exposure) and haemosiderosis in rat lymph nodes (the latter not considered a serious risk in humans). There was no evidence of genotoxicity or carcinogenicity but reproductive studies showed decreased mating and fertility in rats at 12 times human exposure. Apixaban was detected in high concentrations in rat milk.

Clinical

Clinical Evaluation

The clinical evaluator reviewed the submitted data, which relies on 26 clinical pharmacology studies and 4 clinical efficacy and safety studies. Extra information was also provided from the APPRAISE-2 study in acute coronary syndrome which was terminated by the data monitoring committee due to an excess of deaths and bleeding with no significant efficacy benefit and a safety update on amyotrophic lateral sclerosis and Guillain Barré syndrome.

The clinical evaluator recommended approval and noted the potential for bleeding as a concern.

Pharmacology

A total of 814 mostly healthy subjects participated in Phase I studies up to 50 mg orally (tenfold higher than the proposed clinical use) and IV as single doses up to 5 mg. Duration of treatment was up to 10 days in some studies. The main findings for apixaban PK following single or multiple oral doses in healthy subjects are that the drug exhibits linear PK over the oral dose range 2.5 mg to 10 mg bd which is well beyond that proposed for therapeutic use (2.5 mg bd) in this indication. Oral bioavailability of apixaban is ~50% while the drug is highly protein bound (~87%). Maximum plasma concentrations were reached within 3 to 4 h after oral dosing. Absorption appeared to primarily occur in the small intestine. Intake with food did not affect apixaban AUC or C_{max} at the 10 mg dose. While apixaban is metabolised by CYP3A4/5, none of the metabolites appear to be pharmacologically active. Apixaban also appears to have minimal potential for inducing or inhibiting CYP enzymes. The main inactive metabolite (BMS-730823 [M1, O-desmethyl apixaban sulfate]) is present at approximately 25% of parent drug concentrations. Apixaban is not extensively distributed to tissues (Vss of ~21 L). Following intravenous administration, the total body clearance (CLT) of apixaban is low, ~55 mL/min (3.3 L/h), with renal clearance accounting for ~ 27% of CLT. Apixaban reaches steady state concentrations after 3 days of dosing, consistent with the $t_{½}$ of approximately 12 hours and twice daily dosing. The effects of extrinsic and intrinsic factors on apixaban PK were well characterized. Generally apixaban does not require dose modification for the following factors: age (older age had a 32% increase in AUC), gender (females had a 15% higher AUC), body weight (<30% change in PK), race, renal impairment (mild had 16% increase in AUC, moderate had 29% increase in AUC, severe had 38% increase in AUC and those with a creatinine clearance of 15mL/min 24 h had a 44% increase in AUC apixaban exposure), mild to moderate hepatic impairment, co-administration of strong inhibitors of both CYP3A4 and P-gp (~2-fold increase apixaban exposure after ketoconazole) or coadministration of strong inducers of either CYP3A4 or P-gp (~50% decrease in apixaban exposure after rifampicin). Apixaban is a substrate for P-gp transporters but did not appear to inhibit P-gp itself. Conversely, a drug that inhibits P-gp led to a 54% increase in apixaban AUC due to inhibition of P-gp meditated efflux of apixaban into the small intestine. Inducers of CYP enzymes and P-gp will likely reduce apixaban exposure. Apixaban daily doses up to 50 mg were not associated with prolongation of the QTc interval. The effects of smoking, diet composition, herbal products and alcohol use on the PK of apixaban have not been studied.

The following findings from the drug interaction studies were noted:

- Ketoconazole: 100% increase in apixaban AUC
- Diltiazem: 40% increase in apixaban AUC
- Naproxen: 55% increase in apixaban AUC
- Rifampicin: 53% decrease in apixaban AUC

- Digoxin: No significant interaction on digoxin AUC
- Aspirin: No significant interaction on aspirin PK
- Clopidogrel: No significant effect on apixaban AUC or clopidogrel PK
- Enoxaparin: No significant effect on apixaban AUC
- Atenolol: No significant effect on apixaban AUC
- Famotidine: No significant effect on apixaban AUC

Anti-FXa activity exhibits a close, direct, linear relationship with apixaban plasma concentration. Apixaban prolongs clotting time measurements such as INR, prothrombin time, and activated partial thromboplastin time but had no direct effect on platelet aggregation. Changes in clotting time measurements were small and variable with 2.5 mg bd. The anti-FXa assay may be useful for monitoring in situations where knowledge of apixaban exposure may help to inform clinical decisions. Apixaban does not exhibit an effect on the QTc interval.

Efficacy

The efficacy data comprised 4 clinical studies. The first two studies were considered pivotal for this application as they used the dose of enoxaparin (40 mg daily) approved for high risk patients undergoing total knee replacement (TKR) and total hip replacement (THR) in Australia. Two other studies conducted predominantly in North America were considered supportive as they both used an enoxaparin comparator dose of 30 mg q12h, as approved for TKR in the USA, which is different to that approved in Australia. All four studies were multicentre, randomised, double blind, double dummy active controlled with enoxaparin (+ warfarin in the Phase II study). Standard efficacy endpoints were:

- Primary endpoint was all VTE (asymptomatic and symptomatic DVT, non-fatal PE) and all cause death
- Key secondary endpoint was Major VTE (adjudicated proximal DVT, non-fatal PE and VTE related death).

This latter endpoint is the recommended endpoint for VTE prevention studies in the TGA-adopted EMA guideline as this is more clinically relevant.[15] The Phase III studies had non-inferiority designs with an upper bound of the 95% CI set at 1.25 which was considered clinically acceptable. Apixaban was given 12-24 hours post surgery.

CV185010 was a supportive Phase II randomised, double blind dose response study in 1217 patients undergoing elective TKR surgery. Eight treatment groups were compared using six doses of apixaban (5, 10 or 20 mg once daily, 2.5, 5 or 10 mg bd), warfarin (INR 1.8-3.0, open label) and enoxaparin (30 mg q12h as per US dosing) for 12±2 days (mean 10.5 days) with 90% completion but 60-70% evaluable for efficacy analysis. Patients were required to undergo bilateral ascending venography with the standard efficacy endpoints except for the secondary endpoint including all cause death. The incidence of the primary endpoint showed a non-significant dose response with 5.5-12.4% for apixaban, 15.6% for enoxaparin and 26.6% for warfarin (p=0.19 for once daily and p=0.13 for twice daily). The secondary endpoint occurred in 0-2.7% of apixaban subjects (1.8% on apixaban 2.5 mg bd), 4.6% of enoxaparin subjects and 1.8% on warfarin. Major bleeding, minor bleeding and potentially significant bleeds indicate a dose response for bleeding with major bleeding the lowest on apixaban 2.5 mg bd, enoxaparin and warfarin (all zero%). The results tended to favour bd dosing over once daily dosing which led to 2.5 mg bd (the lowest dose studied) being selected as the optimal dose.

[15] EMEA, Committee for Proprietary Medicinal Products (CPMP), 29 June 2000. Points to Consider on Clinical Investigation of Medicinal Products for Prophylaxis and Intra- and Post-operative Venous Thromboembolic Risk, CPMP/EWP/707/98.

CV185047 was a pivotal Phase III randomised, double blind, double dummy, multicentre, active controlled study in 3057 patients (>70% from Europe) undergoing elective TKR surgery comparing apixaban 2.5 mg bd with enoxaparin 40 mg once daily subcutaneously for 11±2 days and 60 days follow up with 91% completion but about 60% evaluable for efficacy analysis. Patients were required to undergo bilateral ascending venography on Day 11 (35-36% missing or non-evaluable) with the standard efficacy endpoints measured. The study had >99% power to demonstrate non-inferiority and 90% power to demonstrate superiority against enoxaparin. The primary efficacy endpoint occurred in 14.88% on apixaban vs 24.76% on enoxaparin with a relative risk reduction of 38% (RR 0.60, 95% CI 0.50, 0.73, p<0.0001 for non-inferiority). Superiority was also demonstrated (p<0.0001). The key secondary endpoint occurred in 1.09% on apixaban vs 2.17% on enoxaparin indicating a relative risk reduction of 50% (RR 0.50, 95% CI 0.26, 0.97) with an absolute risk difference of 1.04%, number needed to treat (NNT) ~96. Secondary endpoints were mostly supportive except for 4 cases of PE on apixaban vs zero on enoxaparin (during follow up there were 3 vs 1 more PE cases) and 2 deaths on apixaban vs zero on enoxaparin (during follow up there was 1 vs 1 more deaths). VTE related death for both periods combined was 2 vs 0. From the data, other endpoints included: symptomatic DVT (0.20 vs 0.46%), all DVT (14.6 vs 24.4%) and proximal DVT symptomatic or asymptomatic (0.76 vs 2.17%) for apixaban vs enoxaparin.

CV185035 was a pivotal Phase III randomised, double blind, double dummy, multicentre, active controlled study in 5406 patients undergoing elective THR surgery comparing apixaban 2.5 mg bd with enoxaparin 40 mg once daily subcutaneously for 35±3 days and 60 days follow up with 90% completion but about 72% evaluable for efficacy analysis. Patients were required to undergo bilateral ascending venography on Day 35 (28-29% missing or non-evaluable) with the standard efficacy endpoints measured. The study had 90% power to demonstrate non-inferiority against enoxaparin. The primary efficacy endpoint occurred in 1.39% on apixaban vs 3.86% on enoxaparin with a relative risk reduction of 64% (RR 0.35, 95% CI 0.20, 0.54, p<0.0001 for non-inferiority). Superiority was also demonstrated (p<0.0001). The key secondary endpoint occurred in 0.45% on apixaban vs 1.14% on enoxaparin indicating a relative risk reduction of 60% (RR 0.40, 95% CI 0.15, 0.80) with an absolute risk difference of 0.68%, NNT ~147. Secondary endpoints showed 3 cases of PE on apixaban vs 5 on enoxaparin (during follow up there were 0 vs 4 more PEs) and 3 deaths on apixaban vs one on enoxaparin (during follow up there were 2 vs 1 more deaths). VTE related death for both periods combined was 1 vs 0. From the data, other endpoints included symptomatic DVT (<0.1 vs 0.2%), all DVT (1.1 vs 3.6%) and proximal DVT symptomatic or asymptomatic (0.3 vs 0.9%) for apixaban vs enoxaparin.

Results were mostly comparable by subgroups of age, gender, region, BMI, race, renal impairment and type of surgery (unilateral or bilateral) with the overall results for both studies. Bleeding rates in subgroups also appeared to be consistent with the overall result.

Besides the supportive Phase II study discussed above, there was one other supportive study submitted which compared apixaban 2.5 mg bd with enoxaparin at a dose of 30 mg q12h, as approved for TKR in the USA, which is different to the approved enoxaparin dose in Australia. This study will therefore only be briefly summarised. An additional study, APPRAISE-2, in acute coronary syndrome will also be briefly summarised but this study is mainly relevant for safety data.

CV185034 was a supportive Phase III randomised, double blind, double dummy, multicentre, active controlled study in 3195 patients undergoing elective TKR surgery comparing apixaban 2.5 mg bd with enoxaparin 30 mg q12h subcutaneously for 12±2 days and 60 days follow up with 88% completion. Patients were required to undergo bilateral

ascending venography on Day 12 (28-29% missing or non-evaluable) with the standard efficacy endpoints measured except for the secondary endpoint including all cause death. The study had 99% power to demonstrate non-inferiority against enoxaparin and 90% power to demonstrate superiority. The primary efficacy endpoint occurred in 8.99% on apixaban vs 8.85% on enoxaparin with a relative risk of 1.02, 95% CI 0.78, 1.32, p=0.0635 for non-inferiority indicating that non-inferiority was not met. The key secondary endpoint occurred in 2.05% on apixaban vs 1.64% on enoxaparin indicating a relative risk of 1.25, 95% CI 0.70, 2.23. Secondary endpoints showed 16 cases of PE on apixaban vs 7 on enoxaparin and 3 deaths on apixaban vs 3 on enoxaparin. Subgroup analysis results were comparable with the overall population.

APPRAISE-2 was a Phase III, randomised, double blind study of 10,800 patients with acute coronary syndrome that compared apixaban at a double dose of 5 mg bd vs placebo for an average of 28 months. More than 80% of patients received dual antiplatelet therapy. The study had 80% power to detect a 20% reduction with apixaban in the primary efficacy endpoint of the composite of cardiovascular death, myocardial infarction or ischaemic stroke. The data monitoring committee stopped the study with less than half the number of required primary endpoints on 14 November 2010 due to excess bleeding events on apixaban. At this stage, 7048 patients had been enrolled. The results are those presented to the DMC which indicate primary events occurred in 200 subjects on apixaban vs 212 subjects on placebo and a projected difference in event rates of 6% rather than the planned 20%. The study failed to demonstrate a benefit for apixaban compared with placebo.

Safety

Safety data were derived from 5,924 patients who received apixaban 2.5 mg bd across the studies with a mean exposure of 34 days in the pivotal hip replacement study (38% of patients) and a mean exposure of 12 days in the pivotal knee replacement study (46% of patients). Adverse events occurred in 64% of apixaban patients and 67% of enoxaparin patients with in general similar safety profiles. Adverse events >5% on apixaban were nausea, constipation, pyrexia, procedural pain, vomiting, oedema, hypotension and dizziness. Stroke and myocardial infarction occurred at similar rates during the pivotal studies on both medications but post-treatment there was a slightly higher MI rate on apixaban (4 vs 1 event) in the hip study but no events in the knee study (0 vs 0 events) however all events occurred >2 weeks post treatment cessation.

All cause death rates were higher in the pivotal clinical studies on apixaban (6 vs 3 deaths in pivotal THR study and 4 vs 0 deaths in the pivotal TKR study) but serious adverse events were similar (6.9 vs 6.5% in the THR study and 4.8 vs 5.8% in the TKR study). Across all 4 studies during the treatment period, death occurred in 10 vs 7 patients with pulmonary embolism the leading cause (5 vs 1 patient). Liver function abnormalities were generally uncommon and similar between both drugs. Potential Hy's law cases occurred in 7 vs 3 patients across the pivotal studies and 1 vs 2 patients across the supportive studies. The evaluator noted that clinically significant LFT abnormalities tended to occur in the perioperative period with associated blood loss, hypotension, infection and multiple concomitant medications. AEs related to LFT elevations were reported in 3.5% on apixaban vs 5.1% on enoxaparin. SAEs related to LFT elevation during the treatment period were reported in four (<0.1%) apixaban subjects and one (<0.1%) enoxaparin subject. AEs related to LFT elevations, during the treatment period and leading to discontinuation were reported for 7 (0.1%) subjects in each treatment group. In general all LFT abnormalities resolved after drug discontinuation and there was no evidence of drug induced liver injury. Laboratory findings including thrombocytopenia, vital signs and ECG abnormalities were similar in both groups. Discontinuations due to adverse events

were also similar (3.4 vs 3.7%). The evaluator noted there were no obvious differences in safety outcomes between subgroups defined by age, gender, race, BMI and body weight, and the overall treatment population.

Bleeding (apixaban 2.5mg bd vs enoxaparin 40mg QD)

In the pivotal Phase III studies, bleeding rates were similar on apixaban 2.5 mg bd and enoxaparin. Half the major bleeding events occurred immediately post-surgery and before the first dose of apixaban.

In the pivotal THR study:

- Major bleeding rates were 0.82 vs 0.68% (adjusted difference 0.15, p=0.54)
- Major or CRNM bleeding rates were 4.83 vs 5.04% (adjusted difference -0.21, p=0.72)

In the pivotal TKR study:

- Major bleeding rates were 0.60 vs 0.93% (adjusted difference -0.33, p=0.30)
- Major or CRNM bleeding rates were 3.53 vs 4.77% (adjusted difference -1.24, p=0.09)

In the supportive TKR study (apixaban 2.5 mg bd vs enoxaparin 30 mg q12h):

- Major bleeding rates were 0.69 vs 1.39% (adjusted difference -0.81, p=0.05)
- Major or CRNM bleeding rates were 2.88 vs 4.28% (adjusted difference -1.46, p=0.03)

No fatal bleeds or intracranial haemorrhages occurred in any apixaban subject in the pivotal trials. Surgical site bleeding rates were similar on both medications (5.73 vs 6.07%).

APPRAISE-2 study

This acute coronary syndrome trial showed a significant excess of bleeding on apixaban vs placebo (17.4 vs 7.6%) including GI bleeding (2.9 vs 1.3%) and intracranial bleeding (10 vs 2 cases) mostly occur in subjects receiving mono or dual antiplatelet therapy. Overall adverse events and serious adverse events had similar rates to placebo. Mortality appeared to worsen with apixaban after ~7 months. LFT abnormalities however were similar to placebo.

Guillain Barré Syndrome (GBS) and Amyotrophic Lateral Sclerosis (ALS)

In the dose ranging Phase II study, there was one case of GBS on apixaban 5 mg QD and one case of ALS on apixaban 10 mg qd. In the Phase III orthopaedic studies, there were no events reported.

Risk Management Plan

The Office of Product Review has accepted the RMP, Version 1 (8 February 2010) for apixaban however has disagreed with the sponsor on some matters. The following outstanding matters remain and should be addressed/accepted in the Pre-ACPM Response and then submitted as an Australian Specific Annex within 30 days of registration:

- Enhanced pharmacovigilance for GBS adverse events in the postmarketing setting that include follow up of all cases with ascertainment of the clinical details of the reaction, diagnosis, clinical investigations, concomitant medications, risk factors, pre-existing disease and outcome. Independent expert evaluations of each case should be included. Cumulative presentation of the events and evaluations should be in the PSUR.
- Suspected drug-drug interaction ADRs should be included in the PSURs in lieu of including this as limited/missing information.

- Serious neurological events should be included in the RMP as a potential safety concern.
- Apixaban use in the very elderly (>75 years old) be included as an ongoing safety concern due to limited information. Routine pharmacovigilance would be acceptable.
- Enhanced pharmacovigilance for bleeding events be implemented upon marketing of apixaban in Australia using a bleeding event data collection form that contains specified information. The form should be submitted for review within 30 days of registration of apixaban.
- The CMI should be included in the packaging as an additional risk minimisation measure to help increase exposure to important information about the risks associated with the use of apixaban, particularly bleeding risk. This view was supported by ACSOM given the increasing availability of oral anticoagulants that do not require specific monitoring and that health professionals and consumers may perceive them as less likely to cause bleeding.

Risk-Benefit Analysis

Delegate Considerations

Efficacy

Apixaban 2.5 mg bd has demonstrated non-inferiority and also superiority in two pivotal well designed Phase III studies against enoxaparin for patients undergoing elective total hip or knee replacement surgery. This efficacy was primarily driven by a reduction in DVT and not a reduction in pulmonary embolism or death. This latter finding is not unexpected given the studies were not powered to demonstrate a difference in these components alone. In the pivotal hip study, PE occurred less on apixaban compared to enoxaparin (3 vs 5 cases) but in the pivotal knee study, the opposite occurred with more PE on apixaban (4 vs 0 cases). In the supportive Phase III study, PE occurred in 16 cases on apixaban vs 7 on enoxaparin which is concerning, however, the opposite trend occurred during the follow up period (one PE occurred in the apixaban group and five in the enoxaparin group). Asymptomatic PE was also not screened for in the studies which may underestimate and skew the data. These rates are low and it is unclear on why they are discordant given also the reduction in DVT demonstrated. The clinical evaluator thought it unlikely to be clinically meaningful with chance being the likely explanation for the results. Approximately 30% of subjects were also not evaluable for the primary endpoint however this was balanced across both groups.

Safety and RMP

The safety profile of apixaban was similar to enoxaparin with no specific safety signals detected. Adverse events, serious adverse events, adverse events leading to discontinuations, laboratory findings, vital signs and ECG abnormalities were similar in both groups. Bleeding related events are the major concern with an anticoagulant and apixaban demonstrated a similar profile to enoxaparin with no fatal bleeds. Bleeding risk did increase with dose and concomitant medications that increase exposure to apixaban could therefore increase the bleeding risk. Myocardial infarction was slightly higher during post-treatment but the numbers were small. Pulmonary embolism was the main cause of death on apixaban but as a serious adverse event not leading to death it had a similar rate to enoxaparin in the two pivotal studies. Deaths were numerically higher overall on apixaban than enoxaparin during treatment and post-treatment periods which is concerning but the numbers were small making it difficult to draw definitive conclusions. Liver function abnormalities mostly occurred in the post-operative setting

and with a low frequency similar to enoxaparin which mostly resolved. The long term APPRAISE-2 study, although in a different population, did not indicate a liver safety signal.

Neurological events

No cases of GBS or ALS occurred in the Phase III orthopaedic studies (one GBS and 1 ALS occurred on apixaban in the Phase II study); they mainly occurred in non-orthopaedic studies. Cases of GBS and ALS were noted to have occurred during ongoing studies. The nonclinical data did not indicate a specific concern in this regard. An expert opinion and review group could not identify a mechanism of action. A comparison with the general population rate showed no statistically significant difference. Nevertheless despite some reassurance from this data, both ACSOM and the clinical evaluator recommend ongoing enhanced surveillance.

Pharmacology and Drug Interactions

The pharmacokinetics of apixaban have been characterised in numerous studies indicating multiple routes of elimination (27% renal, 73% non-renal) and a low propensity thus far for significantly affecting the pharmacokinetics of concomitantly administered medications. Dose reduction did not appear to be required in a number of groups. Apixaban is a substrate for CYP3A4/5 and P-gp but did not appear to induce or inhibit CYP enzymes or inhibit P-gp transporters. Blood samples were collected for future pharmacogenetic analyses but were not considered necessary at this time due to multiple elimination pathways for apixaban. The main interaction finding was with ketoconazole that led to a 100% increase in exposure for apixaban and therefore could be affected by coadministration of strong inhibitors of both CYP3A4 and P-gp. Given the increased bleeding risk demonstrated in the dose ranging study at 5 mg bd and the APPRAISE-2 study supporting an unacceptable bleeding risk at 5 mg bd then apixaban should not be used in patients on strong inhibitors of both CYP3A4 and P-gp. This was commented on by the RMP evaluator and the sponsor has modified the Precautions section of the PI to recommend against its use.

Data deficiencies

There was a lack of long term safety data but the indication is only for short term use. There was no data in severe hepatic impairment and limited information in severe renal impairment. No patients with fractures were assessed as all surgeries were elective procedures. No dose of apixaban lower than 2.5 mg bd was assessed. There is limited information on overdose, although the half life is 12 hours. There is no antidote and a lack of a definitive method for monitoring its anticoagulant effect. The dose ranging study did not include an enoxaparin 40 mg dose due to the consensus at the time of study design that there was no difference in efficacy between it and the 30mg q12h dose. There is also a lack of information on when to cease and restart antiplatelet therapies.

Summary

Overall the submission appears approvable with demonstrated efficacy that is superior to enoxaparin with an acceptable safety profile including the risk of bleeding. The advice of the ACPM was requested on the PE findings and slightly higher number of deaths on apixaban.

The Delegate proposed to approve the submission for the indication:

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

The sponsor should address the following issues in the pre-ACPM response:

- Provide an outline of what further studies are being conducted or proposed in patients with severe renal or severe hepatic impairment.
- Provide an overview of the potential Hy's law cases and the explanation for their likely cause.
- Provide a summary table of the frequency of pulmonary embolism cases across the four clinical studies in both groups in both treatment and post-treatment periods.

Response from Sponsor

The sponsor addressed each of the Delegate's concerns.

Patients with Severe Renal or Severe Hepatic Impairment

The sponsor indicated it was conducting a single dose study (CV 185087) in the USA (first patient first visit expected in mid 2011) to evaluate the pharmacokinetics, pharmacodynamics and safety of apixaban in subjects on haemodialysis. Additional information will be available in the renal impairment population as atrial fibrillation and VTE treatment studies allowed enrolment of patients with severe renal impairment (CrCl cutoff 25mL/min). No studies in severe hepatic impairment are planned.

Potential Hy's Law Cases

Identification and review of potential Hy's Law cases have been integral parts of the apixaban liver safety program. Numerous experts have emphasised that other causes of liver function test (LFT) abnormalities must be investigated and excluded before a diagnosis of Drug-Induced Liver Injury (DILI) can be made.[16,17] The clinical details of potential Hy's law cases (concurrent elevations of ALT > 3 x ULN and total bilirubin > 2 x ULN) in the apixaban development program have been carefully reviewed to identify cases of potential DILI. In CV185035 (hip) and CV185047 (knee), several apixaban treated subjects had post-operative LFT elevations before the first dose of apixaban was given, thus eliminating the possibility that apixaban was the causative factor for the elevations. Review of the potential Hy's law cases illustrates that the subjects in both treatment groups often had hypotension, substantial perioperative blood loss, infection, and administration of numerous concomitant medications, all of which can contribute to the observed generally transient and asymptomatic elevations of LFTs.

A brief narrative for each of the 13 potential Hy's Law cases (apixaban 8, enoxaparin 5) with onset during the Treatment Period in any of the 4 VTEp studies (CV185035, CV185047, CV185034, and CV185010) was provided in the original submission and attached to this response. External hepatologist reviews of these cases were performed blinded to study treatment assignment.

An overview of the potential Hy's Law cases and their likely cause was presented, including the external hepatologists' assessment of relationship to blinded study treatment.

In all of the potential Hy's Law cases in the four VTEp studies, a number of confounding factors were present, such as hypotension, administration of concomitant medications and infection.

Because of these potentially causative factors, none of these cases was considered as an indication of an increased risk of DILI associated with apixaban.

[16] Lewis JH. Hy's law, the Rezulin Rule, and other predictors of severe drug-induced hepatotoxicity: Putting risk-benefit into perspective. Pharmacoepidemiol Drug Safety 2006; 15: 221-229.

[17] Abboud G, Kaplowitz N. Drug-induced liver injury. Drug Safety 2007; 30: 277-294.

Most drugs that are associated with DILI are also associated with an increased frequency of asymptomatic elevation of ALT > 3 x ULN. In the four VTEp studies, the frequency of ALT > 3 x ULN elevations was lower in the apixaban group compared with the enoxaparin group in three of the four studies. In CV185047 (knee), the frequency of ALT elevations > 3 x, 5 x, or 10 x ULN was similar in the two treatment groups, suggesting no increased risk of ALT elevation due to apixaban. No signal of DILI associated with apixaban has been noted in the large atrial fibrillation and acute coronary syndrome (ACS) studies in which over 23,000 subjects received blinded study drug chronically.

In conclusion, the totality of available safety data confirms the hepatic safety profile of apixaban.

While analysis of single case safety data after orthopaedic surgery is complicated by the presence of factors such as use of general anaesthesia, numerous concomitant medications, intraoperative hypotension, transfusions, and infections, no evidence of a risk of hepatotoxicity due to apixaban has been identified. This conclusion is further strengthened by the favourable safety profile of apixaban during long-term administration in the large atrial fibrillation and ACS studies.

Pulmonary Embolism and Cases of Death

As requested by the Delegate, a summary table of the frequency of pulmonary embolism (PE) cases across the four clinical studies in both groups in both treatment and post-treatment periods was provided.

In each of the apixaban and enoxaparin groups there were 10 subjects with PEs during the combined Intended Treatment and Follow up Periods for the 2 pivotal studies. There were fewer PEs in subjects randomised to apixaban than enoxaparin in CV185035 (THR), whereas in CV185047 (TKR), there were more PEs in subjects randomised to apixaban than enoxaparin.

Discrepant results of this nature are not uncommon for low frequency events such as PE, and associated 95% confidence intervals are wide, reflecting the large variability associated with these estimates. As discussed in the sponsor's *Clinical Overview*, similar observations have been made in studies with other recently approved oral anticoagulants. When considering the combined Intended Treatment and Follow up Periods for the two supportive studies, there were a total of 18 subjects with PE in the apixaban 2.5 mg bd group and 13 in the enoxaparin 30 mg q12h group.

As noted by the Delegate, asymptomatic PE was not subject to screening, which may underestimate or skew the data. As in other anticoagulant development programs, detection of PE events relied on reporting of symptoms, which are neither sensitive nor specific, prior to performing any objective diagnostic tests.

Similar to PE, the occurrence of VTE related death, or death due to any cause was also rare in the studies of apixaban in THR and TKR. The 95% confidence intervals for incidence rates of PE, VTE related death, and all cause death for the apixaban and enoxaparin groups overlap by a large margin. The small number of events does not allow for a meaningful assessment of the effect of apixaban relative to enoxaparin on PE or all cause death alone. The sponsor conducted an extensive analysis of clinical data to understand the numerically higher incidence of PE and VTE related deaths reported in the TKR studies in the apixaban treated patients compared to enoxaparin treated patients. These analyses do not provide any explanation for the apparent imbalance in VTE-related deaths and PE events between apixaban and enoxaparin. The conclusion of the sponsor as well as that of the clinical evaluator was that this imbalance is likely due to chance and unlikely to be clinically meaningful.

Pharmacology and Drug Interactions

The Delegate commented that "Given the increased bleeding risk demonstrated in the dose ranging study at 5 mg bd and the APPRAISE-2 study supporting an unacceptable bleeding risk at 5 mg bd then apixaban should not be used in patients on strong inhibitors of both CYP3A4 and P-gp." Whilst the sponsor added a contraindication in the proposed Product Information for such concomitant therapy in patients undergoing orthopaedic surgery, it provided the following clarification:

As described in the response to one of the RMP questions, the apixaban exposure response relationship for any bleeding based on the totality of the data from VTEp efficacy/safety studies is relatively flat across the range of exposures associated with total daily apixaban doses of 5 to 10 mg. Thus, the bleeding risk for apixaban 5 mg bd in the VTEp population is estimated to be only about 18% higher than that for 2.5 mg bd and similar to the bleeding risk for the current standard of care enoxaparin 40 mg qd.

Furthermore, as pointed out in the responses to other RMP questions, the sponsor believed that the bleeding results from the APPRAISE-2 study are specific to the patient population in that study and cannot be used to determine the bleeding risk associated with a 5 mg bd dose in the VTEp population. The APPRAISE-2 study was designed to investigate the efficacy and safety of apixaban 5 mg bd compared to placebo in patients with recent ACS who had at least 2 additional risk factors (for example, previous stroke, heart failure, renal failure). Most patients (approximately 80%) were administered apixaban concomitantly with both aspirin and clopidogrel, whereas antiplatelet therapy is routinely discontinued before elective surgical procedures such as hip or knee replacement, except in patients with an increased risk of cardiovascular events for whom the benefit of this therapy is expected to outweigh the bleeding risk. In addition, the duration of therapy was longer than for VTEp.

In their recommendation to stop the APPRAISE-2 study, the Data Monitoring Committee noted:

"The members of the APPRAISE-2 DMC wish to emphasize that this recommendation concern only patients with ACS, receiving mono- or dual antiplatelet therapy. Other trials have demonstrated the value of apixaban in patients with deep vein thrombosis and patients after orthopaedic surgery and address the use of apixaban in patients with atrial fibrillation. The current recommendation to stop APPRAISE-2 does not concern these patients."

In addition, a study of patients with atrial fibrillation comparing apixaban to warfarin is underway, being monitored by an independent DMC, and is continuing unchanged.

Therefore, the sponsor did not agree with the statement that there is an unacceptable bleeding risk with apixaban 5 mg bd, other than in high risk patients with recent ACS receiving mono or dual antiplatelet therapy.

Risk Management Plan (RMP)

Outstanding matters from the assessment of the RMP and of the sponsor's responses were addressed, as requested by the Office of Product Review. The sponsor committed to provide an updated RMP with an Australian specific annex within 30 days of registration.

During the first year post approval, subject to appropriate review/modification depending on findings after that time period, the sponsor indicated it would perform enhanced pharmacovigilance for identified GBS events in the postmarketing setting that includes: follow up of all cases with ascertainment of the clinical details of the reaction, diagnosis, clinical investigations, concomitant medications, risk factors, pre-existing disease and

outcome; independent expert evaluations and cumulative presentation of identified GBS events and evaluations in the PSUR.

As is standard practice for the sponsor, the sponsor agreed to review suspected drug-drug interaction ADRs in the PSUR.

The sponsor agreed to consider identified GBS cases as an important potential risk in the RMP with the postmarketing plan as outlined above.

The sponsor maintained that apixaban has been adequately studied in the elderly population. A total of 945 subjects ≥ 75 years of age received apixaban 2.5 mg bd across all four VTEp studies which is 16% of all apixaban treated subjects. Three hundred and twenty three (12.1%) subjects in the apixaban arm were very elderly (age > 75 years) in the THR study and a total of 622 (>19%) subjects were very elderly in the apixaban treated groups in the TKR studies.

Overall, among elderly subjects, no clinically relevant differences between treatment groups were noted. These numbers of patients are well within the spirit of ICH guideline E1, even though apixaban is currently intended for short term use and the sponsor therefore does not believe that use in the very elderly should be included as an ongoing safety concern due to limited information.

Enhanced pharmacovigilance for bleeding events will include a "Bleeding Event Request for Data" form that contains the information specified by the OPR.

Finally, the sponsor agreed to include the CMI in the packaging.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

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

The ACPM agreed with the Delegate that there were no quality, pharmaceutical chemistry or nonclinical concerns and that the demonstrated efficacy is superior to the active comparator, enoxaparin. The safety data suggested the product also showed an acceptable safety profile including the risk of bleeding. The ACPM considered there is a favourable benefit risk profile for this product.

The risk of bleeding and the incidence of Guillain-Barré syndrome were considered to be adequately addressed in the PI/CMI and in the RMP.

The ACPM also recommended changes to the proposed PI and Consumer Medicines Information (CMI) but these are beyond the scope of this AusPAR.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Eliquis containing apixaban 2.5 mg, indicated for:

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

Among the specific conditions of registration were the following:

- The implementation in Australia of the apixaban Risk Management Plan (RMP) version 1, and the agreed changes and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

- The provision of an updated RMP with an Australian specific annex within 30 days of registration.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

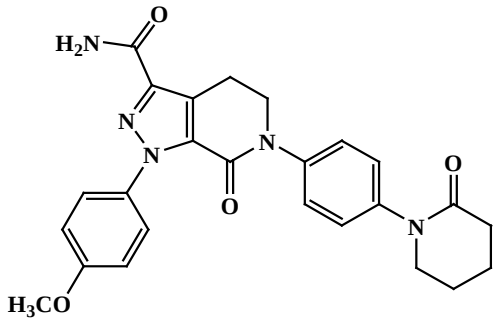
PRODUCT INFORMATION

ELIQUIS®

apixaban

NAME OF THE MEDICINE

Apixaban, a selective inhibitor of the coagulation factor Xa (FXa), 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:



CAS Number: 503612-47-3

DESCRIPTION

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. The octanol/water partition coefficient is 44.7 at pH 7.4.

ELIQUIS film-coated tablets are available for oral administration in the strength of 2.5 mg of apixaban with the following inactive ingredients: anhydrous lactose, cellulose - microcrystalline, croscarmellose sodium, sodium lauryl sulfate, and magnesium stearate. The film coating contains lactose monohydrate, hypromellose, titanium dioxide, glycerol triacetate and yellow iron oxide.

PHARMACOLOGY

Pharmacodynamics

The pharmacodynamic effects of apixaban are reflective of the mechanism of action (FXa inhibition). 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 are small and subject to a

high degree of variability. They are not recommended to assess the pharmacodynamic effects of apixaban.

Apixaban also demonstrates anti-FXa activity as evident by reduction in Factor Xa enzyme activity in the Rotachrom® Heparin chromogenic assay. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban, and precision of the Rotachrom® assay is well within acceptable limits for use in a clinical laboratory. The dose- and concentration-related changes observed following apixaban administration are more pronounced, and less variable, with anti-FXa activity compared with clotting tests.

Predicted steady-state peak and trough anti-FXa activity with apixaban 2.5 mg twice daily dosing are 1.3 IU/mL (5th/95th percentile 0.67-2.4 IU/mL) and 0.84 IU/mL (5th/95th percentile 0.37-1.8 IU/mL), respectively, demonstrating less than a 1.6-fold fluctuation in peak-to-trough anti-FXa activity over the dosing interval.

Although treatment with apixaban at the recommended dose does not require routine monitoring of exposure, the Rotachrom® anti-FXa assay may be useful in exceptional situations where knowledge of apixaban exposure may help to inform clinical decisions, e.g. overdose or emergency surgery.

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

Mechanism of Action

Apixaban is a reversible, direct and highly selective inhibitor of factor Xa. It does not require antithrombin III for antithrombotic activity. Apixaban inhibits free and clot-bound factor Xa, and prothrombinase activity. Apixaban has no direct effects on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting factor Xa, apixaban prevents thrombin generation and thrombus development. Preclinical studies of apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that caused negligible prolongation of prothrombin time and bleeding time in rabbits and dogs, but more than 2-fold increases in prothrombin time and bleeding time in rats.

Pharmacokinetics

Absorption

The absolute bioavailability of apixaban is approximately 50% for doses up to 10 mg. Apixaban is rapidly absorbed with maximum concentrations (Cmax) appearing 3 to 4 hours after tablet intake. Intake with food does not affect apixaban AUC or Cmax at the 10 mg dose. Apixaban can be taken with or without food. Apixaban demonstrates linear pharmacokinetics with dose proportional increases in exposure for oral doses up to 10 mg. At

doses ≥ 25 mg apixaban displays dissolution limited absorption with decreased bioavailability. Apixaban exposure parameters exhibit low to moderate variability reflected by a within-subject and inter-subject variability of ~ 20% CV and ~ 30% CV, respectively.

Distribution

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

Metabolism and Elimination

Apixaban has multiple routes of elimination. Of the administered apixaban dose in humans, approximately 25% was recovered as metabolites, with the majority recovered in faeces. Renal excretion of apixaban accounts for approximately 27% of total clearance. Additional contributions from biliary and direct intestinal excretion were observed in clinical and nonclinical studies, respectively.

Apixaban has a total clearance of about 3.3 L/h and a half-life of approximately 12 hours.

O-demethylation and hydroxylation at the 3-oxopiperidinyl moiety are the major sites of biotransformation. Apixaban is metabolised mainly via CYP3A4/5 with minor contributions from CYP1A2, 2C8, 2C9, 2C19, and 2J2. Unchanged apixaban is the major drug-related component in human plasma with no active circulating metabolites present. Apixaban is a substrate of transport proteins, P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP).

Special Populations

Elderly (>65 years)

Elderly patients (above 65 years) exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 32% higher. No dose adjustment is required.

Children and Adolescents

The efficacy and safety of ELIQUIS in children below age 18 have not yet been established. No data are available.

Gender

Exposure to apixaban was approximately 18% higher in females than in males. No dose adjustment is required.

Race

The results across phase 1 studies showed no discernible difference in apixaban pharmacokinetics between White/Caucasian, Asian and Black/African American subjects. Findings from a population pharmacokinetic analysis in patients who received apixaban following elective hip or knee replacement surgery were consistent with the phase 1 results. No dose adjustment is required.

Body Weight

Compared to apixaban exposure in subjects with body weight of 65 to 85 kg, body weight > 120 kg was associated with approximately 30% lower exposure and body weight < 50 kg was associated with approximately 30% higher exposure. No dose adjustment is required.

Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment (see DOSAGE AND ADMINISTRATION, Use in Renal Impairment and PRECAUTIONS, Use in Renal Impairment). There is no clinical experience available in patients with creatinine clearance <15 mL/min or in patients undergoing dialysis, therefore apixaban is contraindicated in these patients (see CONTRAINDICATIONS).

There was no impact of impaired renal function on peak concentration of apixaban. There was an increase in apixaban exposure correlated to decrease in renal function, as assessed via measured creatinine clearance. In individuals with mild (creatinine clearance 51 – 80 mL/min), moderate (creatinine clearance 30 – 50 mL/min) and severe (creatinine clearance 15 - 29 mL/min) renal impairment, apixaban plasma concentrations (AUC) were increased 16, 29, and 44% respectively, compared to individuals with normal creatinine clearance. Renal impairment had no evident effect on the relationship between apixaban plasma concentration and anti-FXa activity.

Hepatic Impairment

Apixaban has not been studied in patients with severe hepatic impairment or active hepatobiliary disease. Apixaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

No dose adjustment is required in patients with mild or moderate hepatic impairment; however, given the limited number of subjects studied, caution is advised when using ELIQUIS in this population (see DOSAGE AND ADMINISTRATION, Use in Hepatic Impairment and PRECAUTIONS, Use in Hepatic Impairment).

In a study comparing subjects with mild and moderate hepatic impairment (classified as Child-Pugh A and B, respectively) to healthy control subjects, the single-dose pharmacokinetics and pharmacodynamics of apixaban 5 mg were not altered in subjects with hepatic impairment. Changes in anti-Factor Xa activity and INR were comparable between subjects with mild to moderate hepatic impairment and healthy subjects.

Pharmacokinetic/Pharmacodynamic Relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship between apixaban plasma concentration and several PD endpoints (anti-FXa activity, INR, PT, aPTT) has been evaluated after administration of a wide range of doses (0.5 - 50 mg). The relationship between apixaban plasma concentration and anti-factor Xa activity was best described by a

linear model. The PK/PD relationship observed in patients who received apixaban following elective hip or knee replacement surgery was consistent with that established in healthy subjects.

CLINICAL TRIALS

The apixaban clinical program was designed to demonstrate the efficacy and safety of apixaban for the prevention of venous thromboembolic events (VTE) in a broad range of adult patients undergoing elective hip or knee replacement. A total of 8,464 patients were randomised in two pivotal, double-blind, multi-national studies, comparing apixaban 2.5 mg given orally twice daily (4,236 patients) or enoxaparin 40 mg once daily (4,228 patients). Included in this total were 1,262 patients (618 in the apixaban group) of age 75 or older, 1,004 patients (499 in the apixaban group) with low body weight $\leq$ 60 kg), 1,495 patients (743 in the apixaban group) with BMI $\geq$33 kg/m^2 and 437 patients with severe or moderate renal impairment (217 patients in the apixaban group). The ADVANCE-3 study included 5,407 patients undergoing elective hip replacement (mean age: 61 years; 53% female), and the ADVANCE-2 study included 3,057 patients undergoing elective knee replacement (mean age: 66 years; 72% female). Apixaban was not studied in patients undergoing hip fracture surgery.

Adult patients scheduled for hip or knee replacement surgery could be enrolled provided they had no active bleeding or high risk of bleeding, no active hepatobiliary disease, their creatinine clearance was not less than 30 mL/min, their ALT or AST level was not greater than twice the upper limit of normal (ULN) and they were not on treatment with medications affecting coagulation or platelet function unless they could be withdrawn.

Subjects received either apixaban 2.5 mg given orally twice daily (po bid) or enoxaparin 40 mg administered subcutaneously once daily (sc od). The first dose of apixaban was given 12 to 24 hours post-surgery, whereas enoxaparin was started 9 to 15 hours prior to surgery. Both apixaban and enoxaparin were given for 32-38 days in the ADVANCE-3 study and for 10-14 days in the ADVANCE-2 study.

Based on patient medical history in the studied population of ADVANCE-3 and ADVANCE-2 (8,464 patients), 46% had hypertension, 10% had hyperlipidemia, 9% had diabetes, and 8% had coronary artery disease.

Efficacy analyses of the pivotal studies utilised a pre-specified testing sequence that allowed testing for superiority on the primary endpoint only after non-inferiority (NI) was established. The NI margin used for the primary endpoint was 1.25, i.e. the upper bound of the 95% confidence interval for the relative risk was not to exceed 1.25. Similarly, testing for superiority on the key secondary endpoint of Major VTE was only conducted after non-inferiority on this endpoint was established.

Apixaban demonstrated a statistically superior reduction in the primary endpoint, a composite of all VTE/all cause death, and in the Major VTE endpoint, a composite of proximal deep vein thrombosis (DVT), non-fatal pulmonary embolism (PE), and VTE-related death, compared to enoxaparin in both elective hip or knee replacement surgery (see Table 1).

Table 1: Efficacy results from pivotal phase III studies

Study	**ADVANCE-3 (hip)**			**ADVANCE-2 (knee)**		
Study treatment Dose Duration of treatment	Apixaban 2.5 mg po bid 35 ± 3 d	Enoxaparin 40 mg sc od 35 ± 3 d	p-value	Apixaban 2.5 mg po bid 12 ± 2 d	Enoxaparin 40 mg sc od 12 ± 2 d	p-value
Total VTE/all-cause death						
Number of events/subjects Event Rate	27/1949 1.39%	74/1917 3.86%	<0.0001	147/976 15.06%	243/997 24.37%	<0.0001
Relative Risk 95% CI	0.36 (0.22, 0.54)			0.62 (0.51, 0.74)		
Absolute Risk Difference 95% CI	-2.47% (-3.54,- 1.50)			-9.27% (-12.74, -5.79)		
Components of primary endpoint[a]						
Distal or proximal DVT Event rate 95% CI	1.13% (0.74, 1.72)	3.56% (2.81, 4.50)		14.62% (12.54, 17.00)	24.37% (21.81, 27.14)	
Non-fatal PE Event rate 95% CI	0.07% (0.00, 0.29)	0.19% (0.07, 0.45)		0.20% (0.04, 0.61)	0.00% (0.00, 0.31)	
All-cause death Event rate 95% CI	0.11% (0.02, 0.35)	0.04% (0.00, 0.24)		0.13% (0.01, 0.52)	0.0% (0.00, 0.31)	
Major VTE						
Number of events/subjects Event Rate	10/2199 0.45%	25/2195 1.14%	0.0107	13/1195 1.09%	26/1199 2.17%	0.0373
Relative Risk 95% CI	0.40 (0.15, 0.80)			0.50 (0.26, 0.97)		
Absolute Risk Difference 95% CI	-0.68% (-1.27,- 0.17)			-1.04% (-2.03, -0.05)		
Components of Major VTE endpoint[a]						
Proximal DVT Event rate 95% CI	0.32% (0.14, 0.68)	0.91% (0.59, 1.42)		0.76% (0.38, 1.46)	2.17% (1.47, 3.18)	
Non-fatal PE Event rate 95% CI	0.07% (0.00, 0.29)	0.19% (0.07, 0.45)		0.20% (0.04, 0.61)	0.00% (0.00, 0.31)	
VTE-related death Event rate 95% CI	0.04% (0.00, 0.24)	0.00% (0.00, 0.18)		0.07% (0.00, 0.42)	0.00% (0.00, 0.31)	

[a] Events associated with each endpoint were counted once per subject but subjects may have contributed events to multiple endpoints

The safety endpoints of major bleeding, the composite of major and clinically relevant non-major (CRNM) bleeding, and all bleeding showed similar rates for patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see Table 2). Major bleeding was defined as a decrease in haemoglobin of 2g/dL or more over a 24 hour period, transfusion of 2 or more units of packed red cells, bleeding into a critical site (e.g., intracranial haemorrhage) or fatal. CRNM bleeding was defined as significant epistaxis, gastrointestinal bleed, significant

haematuria, significant haematoma, bruising or ecchymosis, or haemoptysis. All the bleeding criteria included surgical site bleeding.

In both Phase III studies, bleeding was assessed beginning with the first dose of double-blind study medication, which was either enoxaparin or injectable placebo, given 9 to 15 hours before surgery. Bleeding during the treatment period included events that occurred before the first dose of apixaban, which was given 12-24 hours after surgery. Bleeding during the post-surgery treatment period only included events occurring after the first dose of study medication after surgery. Over half the occurrences of major bleeding in the apixaban group occurred prior to the first dose of apixaban. Table 2 shows the bleeding results from the treatment period and the post-surgery treatment period.

Table 2: Bleeding results from pivotal phase III studies†

	ADVANCE-3		**ADVANCE-2**	
	Apixaban 2.5 mg po bid 35 ± 3 d	**Enoxaparin 40 mg sc od 35 ± 3 d**	**Apixaban 2.5 mg po bid 12 ± 2 d**	**Enoxaparin 40 mg sc od 12 ± 2 d**
All treated	n = 2673	n = 2659	n = 1501	n = 1508
Treatment Period				
Major	22 (0.8%)	18 (0.7%)	9 (0.6%)	14 (0.9%)
Fatal	0	0	0	0
Major + CRNM	129 (4.8%)	134 (5.0%)	53 (3.5%)	72 (4.8%)
All	313 (11.7%)	334 (12.6%)	104 (6.9%)	126 (8.4%)
Post-surgery treatment period				
Major	9 (0.3%)	11 (0.4%)	4 (0.3%)	9 (0.6%)
Fatal	0	0	0	0
Major + CRNM	96 (3.6%)	115 (4.3%)	41 (2.7%)	56 (3.7%)
All	261 (9.8%)	293 (11.0%)	89 (5.9%)	103 (6.8%)

† all the bleeding criteria included surgical site bleeding

In a clinical study in high risk acute coronary syndrome patients, as characterised by advanced age and multiple cardiac and non-cardiac co-morbidities (e.g., diabetes, heart failure), receiving apixaban 5 mg twice daily versus placebo, a significant increase in bleeding risk, including gastrointestinal and intracranial bleeding, was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel (see INTERACTIONS WITH OTHER MEDICINES, Effect of Other Medicines on apixaban).

INDICATIONS

ELIQUIS is indicated for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery.

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients:

- with hypersensitivity to apixaban or to any of the excipients;
- with clinically significant active bleeding (such as intracranial and gastrointestinal bleeding) and in patients with spontaneous or pharmacological impairment of haemostasis;
- with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see PHARMACOLOGY, Pharmacokinetics);
- with severe renal impairment with a creatinine clearance < 15 mL/min (see PHARMACOLOGY, Pharmacokinetics);
- with organ lesions at risk of clinically significant bleeding, including haemorrhagic stroke within the last 6 months;
- receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g., ketoconazole) or HIV protease inhibitors (e.g., ritonavir) (see INTERACTIONS WITH OTHER MEDICINES).

PRECAUTIONS

Haemorrhage Risk

Patients taking ELIQUIS are to be carefully observed for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. ELIQUIS is recommended to be used with caution in conditions with increased risk of haemorrhage, such as: congenital or acquired bleeding disorders; active ulcerative gastrointestinal disease; bacterial endocarditis; thrombocytopenia; platelet disorders; history of haemorrhagic stroke; severe uncontrolled hypertension; and recent brain, spinal, or ophthalmological surgery. ELIQUIS administration should be discontinued if severe haemorrhage occurs (see OVERDOSAGE).

In the event of haemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. The initiation of appropriate treatment, e.g., surgical haemostasis or the transfusion of fresh frozen plasma should be considered. If life-threatening bleeding cannot be controlled by the above measures, administration of recombinant factor VIIa may be considered. However, there is currently no experience with the use of recombinant factor VIIa in individuals receiving apixaban. Re-dosing of recombinant factor VIIa could be considered and titrated depending on improvement of bleeding.

Renal Impairment

Because there is no clinical experience in patients with creatinine clearance < 15 mL/min or in patients undergoing dialysis, apixaban is contraindicated in these patients (see CONTRAINDICATIONS). Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 mL/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore, apixaban is to be used with caution in these patients. No dose adjustment is necessary in patients with mild or moderate renal impairment (see DOSAGE AND ADMINISTRATION, Use in Renal Impairment and PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment

ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B) (see DOSAGE AND ADMINISTRATION, Use in Hepatic Impairment and PHARMACOLOGY, Pharmacokinetics).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin 1.5 x ULN were excluded in clinical trials. Therefore ELIQUIS should be used cautiously in this population. ALT should be measured as part of the standard pre-operative evaluation.

Interaction with Other Medicines affecting Haemostasis

Care is to be taken if patients are treated concomitantly with non-steroidal anti-inflammatory drugs (NSAIDs), including acetylsalicylic acid, because these medicines may impact haemostasis. Other platelet aggregation inhibitors or other antithrombotic agents are not recommended concomitantly with ELIQUIS due to an increased risk in bleeding reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with recent acute coronary syndrome (see INTERACTIONS WITH OTHER MEDICINES and CLINICAL TRIALS).

Spinal/Epidural Anaesthesia or Puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) 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 haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of ELIQUIS. The risk may also be increased by traumatic or repeated epidural or spinal puncture. Patients are to be frequently monitored 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.

There is no clinical experience with the use of apixaban with indwelling intrathecal or epidural catheters. In case of such need and based on Pharmacokinetic data, a time interval of 20-30 hours (i.e., twice the half-life) between the last dose of apixaban and catheter withdrawal should elapse, and at least one dose should be omitted before catheter withdrawal. The next dose of apixaban may be given at least 5 hours after catheter removal. Experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in the presence of neuraxial blockade.

Hip Fracture Surgery

Apixaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, ELIQUIS is not recommended in these patients.

Effects on Fertility

Studies in adult rats dosed with apixaban at up to 600 mg/kg/day (up to 10 times the clinical exposure based on free fraction AUC) showed no effect on fertility. In the offspring of rats treated with apixaban from gestation day 6 to lactation day 20, there were decreases in female mating and fertility at≥ 200 mg/kg/day (12 times the human exposure based on free fraction AUC). Fertility of the female offspring was unaffected at the maternal dose of 25 mg/kg/day (3 times the human exposure). There were no effects on mating or fertility of male offspring at ≥ 1000 mg/kg/day (13 times the human exposure based on free fraction AUC). Plasma apixaban concentrations in the offspring were not measured, but high apixaban concentrations (30 times the maternal plasma AUC) were detected in milk.

Use in Pregnancy

Category C

Anticoagulants and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. There are limited data from the use of apixaban in pregnant women. Apixaban is not recommended during pregnancy.

Embryo-foetal development studies at oral doses up to 1500, 3000 and 1500 mg/kg/day in mice, rats and rabbits, respectively, and IV doses up to 5 mg/kg/day in rabbits showed no evidence of effects on embryo-foetal development in the 3 animal species tested. Maternal exposures to apixaban in the animal studies were 56 times (mouse), 12 times (rat) and once (rabbit) the human exposure, based on free fraction AUC. Very low exposure to apixaban was detected in the foetus (8-11% of the maternal plasma concentration in mice, 7% in rats and <1% in rabbits).

Use in Lactation

There are no human data on the excretion of apixaban in milk. Apixaban is a substrate of BCRP, an active transporter expressed in tissues including mammary gland alveolar epithelium. Available data in animals have shown excretion of apixaban in rat milk (milk/plasma ratio: 30). Apixaban may be excreted in human milk and a risk to newborns and infants cannot be excluded. A decision must be made to either discontinue breast-feeding or to discontinue/abstain from apixaban therapy.

In a pre/postnatal study in rats dosed from gestation day 6 to postnatal day 20, mating and fertility of female offspring were reduced (see Effects on Fertility). Otherwise, postnatal development was unaffected at maternal doses up to 1000 mg/kg/day, with exposures up to 13 times the human exposure based on free fraction AUC.

Paediatric Use

The efficacy and safety of ELIQUIS in children below age 18 have not yet been established. No data are available.

Use in the Elderly

No dose adjustment is necessary in elderly patients. Of the total number of subjects in clinical studies of apixaban, 50% were 65 and older, while 16 %were 75 and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

There is limited clinical experience in elderly patients co-administered ELIQUIS with acetylsalicylic acid. This combination should be used cautiously because of a potentially higher bleeding risk.

Genotoxicity

Apixaban did not induce gene mutations in bacteria (*Salmonella typhimurium*) or chromosomal damage in mammalian cells (Chinese hamster ovary cells) *in vitro* and lymphocytes in rats *in vivo*. There was no evidence of genotoxic potential in a micronucleus test in rats. The oral doses in the rat lymphocyte chromosome aberration study at up to 600 mg/kg/day for 30 days resulted in plasma apixaban concentrations 14 times the human value based on free fraction Cmax.

Carcinogenicity

Long term studies in mice and rats at dietary doses up to 3000 and 600 mg/kg/day, respectively, did not show any evidence of carcinogenic potential. These doses resulted in plasma apixaban concentrations 42 times (mice) and 8 times (rat) human values at 2.5 mg twice daily based on free fraction AUC.

Effects on Laboratory Tests

Clotting tests (e.g. PT, INR, and aPTT) are affected as expected by the mechanism of action of apixaban (see PHARMACOLOGY, Mechanism of Action). Changes observed in these clotting tests at the expected therapeutic dose are small and subject to a high degree of variability (see PHARMACOLOGY, Pharmacodynamics).

Effects on Ability to Drive and Use Machines

ELIQUIS has no or negligible influence on the ability to drive and use machines.

INTERACTIONS WITH OTHER MEDICINES

Apixaban is eliminated by renal and non-renal pathways, including metabolism and biliary excretion. Metabolism occurs mainly via CYP3A4/5. Apixaban is a substrate of transport proteins, P-gp and BCRP (see PHARMACOLOGY, Pharmacokinetics).

Effect of Other Medicines on apixaban

Inhibitors of CYP3A4 and P-gp

Co-administration of apixaban with ketoconazole (400 mg once a day), a strong inhibitor of both CYP3A4 and P-gp, led to a 2-fold increase in mean apixaban AUC and a 1.6-fold increase in mean apixaban Cmax. Such increases in apixaban plasma concentrations may lead to an increased bleeding risk and, therefore, apixaban is contraindicated in patients who have undergone orthopaedic surgery and are receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as systemic treatment with azole-antimycotics (e.g., ketoconazole, itraconazole, voriconazole or posaconazole) or HIV protease inhibitors (e.g., ritonavir) (see CONTRAINDICATIONS).

Active substances moderately inhibiting the apixaban elimination pathways, CYP3A4 and/or P-gp, are expected to increase apixaban plasma concentrations to a lesser extent. Diltiazem (360 mg once a day), for instance, considered a moderate CYP3A4 and a weak P-gp inhibitor, led to a 1.4-fold increase in mean apixaban AUC and a 1.3-fold increase in Cmax. Naproxen (500 mg, single dose) an inhibitor of P-gp but not an inhibitor of CYP3A4, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and Cmax, respectively. No dose adjustment for apixaban is required when co-administered with less potent inhibitors of CYP3A4 and/or P-gp.

Inducers of CYP3A4 and P-gp

Co-administration of apixaban with rifampin, a strong inducer of both CYP3A4 and P-gp, led to an approximate 54% and 42% decrease in mean apixaban AUC and Cmax, respectively. The concomitant use of apixaban with other strong CYP3A4 and P-gp inducers (e.g., phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during

concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution.

Anticoagulants, platelet aggregation inhibitors and NSAIDs

After combined administration of enoxaparin (40 mg single dose) with apixaban (5 mg single dose), an additive effect on anti-Factor Xa activity was observed.

Pharmacokinetic or pharmacodynamic interactions were not evident in healthy subjects when apixaban was co-administered with acetylsalicylic acid 325 mg once a day.

Apixaban co-administered with clopidogrel (75 mg once a day) or with the combination of clopidogrel 75 mg and acetylsalicylic acid 162 mg once daily in phase 1 studies did not show a relevant increase in bleeding time, further inhibition of platelet aggregation, or increase of clotting tests (PT, INR, and aPTT) compared to administration of the antiplatelet agents without apixaban.

Naproxen (500 mg), an inhibitor of P-gp, led to a 1.5-fold and 1.6-fold increase in mean apixaban AUC and Cmax in healthy subjects, respectively. Corresponding increases in clotting tests were observed for apixaban. No changes were observed in the effect of naproxen on arachidonic acid-induced platelet aggregation and no clinically relevant prolongation of bleeding time was observed after concomitant administration of apixaban and naproxen.

Despite these findings, ELIQUIS should be used with caution when co-administered with NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome. Agents associated with serious bleeding are not recommended concomitantly with ELIQUIS, such as: unfractionated heparins and heparin derivatives (including low molecular weight heparins (LMWH)), factor Xa inhibiting oligosaccharides (e.g., fondaparinux), direct thrombin II inhibitors (e.g., bivalirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, thienopyridines (e.g., clopidogrel), dipyridamole, dextran, vitamin K antagonists, and other oral anticoagulants. It should be noted that unfractionated heparin can be administered at doses necessary to maintain a patent central venous or arterial catheter (see INTERACTIONS WITH OTHER MEDICINES, Interaction with Other Medicines affecting Haemostasis).

Other Concomitant Therapies

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when apixaban was co-administered with atenolol or famotidine. Co-administration of apixaban 10 mg with atenolol 100 mg did not have a clinically relevant effect on the pharmacokinetics of apixaban. Following administration of the two drugs together, mean apixaban AUC and Cmax were 15% and 18% lower than when administered alone. The administration of apixaban 10 mg with famotidine 40 mg had no effect on apixaban AUC or Cmax.

Paediatric Population

Interaction studies have only been performed in adults.

Effect of apixaban on Other Medicines

In vitro apixaban studies showed no inhibitory effect on the activity of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2D6 or CYP3A4 (IC50 > 45 μM) and weak inhibitory effect on the activity of CYP2C19 (IC50 > 20 μM) at concentrations that are significantly greater than peak plasma concentrations observed in patients. Apixaban did not induce CYP1A2, CYP2B6, CYP3A4/5 at a concentration up to 20 μM. Therefore, apixaban is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Apixaban is not a significant inhibitor of P-gp.

In studies conducted in healthy subjects, as described below, apixaban did not meaningfully alter the pharmacokinetics of digoxin, naproxen, or atenolol.

Digoxin

Coadministration of apixaban (20 mg once a day) and digoxin (0.25 mg once a day), a P-gp substrate, did not affect digoxin AUC or Cmax. Therefore, apixaban does not inhibit P-gp mediated substrate transport.

Naproxen

Coadministration of single doses of apixaban (10 mg) and naproxen (500 mg), a commonly used NSAID, did not have any effect on the naproxen AUC or Cmax.

Atenolol

Coadministration of a single dose of apixaban (10 mg) and atenolol (100 mg), a common beta-blocker, did not alter the pharmacokinetics of atenolol.

ADVERSE EFFECTS

The safety of apixaban has been evaluated in one phase II and three phase III studies including 5,924 patients exposed to apixaban 2.5 mg twice daily undergoing major orthopaedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days. Of these, 2,673 patients undergoing hip replacement were treated for a mean duration of 34 days and 3,251 patients undergoing knee replacement were treated for a mean duration of 10 and 12 days in the phase II and III studies, respectively.

In total, 11% of the patients treated with apixaban 2.5 mg twice daily experienced adverse reactions. Bleeding may occur during apixaban therapy in the presence of associated risk factors such as organic lesions liable to bleed. Common adverse reactions were anaemia, haemorrhage, contusion and nausea. The overall incidences of adverse reactions of bleeding, anaemia and abnormalities of transaminases (e.g., alanine aminotransferase levels) were

similar between treatment groups in the phase II and phase III studies in elective hip and knee replacement surgery. The adverse reactions should be interpreted within the surgical setting.

The use of ELIQUIS may be associated with an increased risk of occult or overt bleeding from any tissue or organ, which may result in posthaemorrhagic anaemia. The signs, symptoms and severity will vary according to the location and degree or extent of the bleeding (see PRECAUTIONS, Haemorrhage Risk and CLINICAL TRIALS). Bleeding was assessed as a safety endpoint in the clinical trials. Similar rates were seen for major bleeding, the composite of major and clinically relevant non-major bleeding, and all bleeding in patients treated with apixaban 2.5 mg compared with enoxaparin 40 mg (see CLINICAL TRIALS, Table 2).

Adverse events from the pivotal phase III studies (ADVANCE-2 and ADVANCE-3) are listed in Table 3 by system organ classification (MedDRA) and by frequency.

Table 3 Common adverse events occurring in≥ 1% of patients in either group undergoing hip or knee replacement surgery, regardless of causality

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Number treated	4174 (100)	4167 (100)
Gastrointestinal disorders		
Nausea	587 (14.1)	649 (15.6)
Constipation	392 (9.4)	441 (10.6)
Vomiting	288 (6.9)	350 (8.4)
Diarrhoea	96 (2.3)	110 (2.6)
Dyspepsia	48 (1.2)	60 (1.4)
Injury, poisoning and procedural complications		
Procedural pain	431 (10.3)	433 (10.4)
Anaemia postoperative	194 (4.6)	196 (4.7)
Contusion	63 (1.5)	86 (2.1)
Procedural hypotension	62 (1.5)	58 (1.4)
Wound secretion	58 (1.4)	54 (1.3)
General disorders and administration site conditions		
Pyrexia	307 (7.4)	313 (7.5)
Oedema peripheral	222 (5.3)	201 (4.8)
Pain	93 (2.2)	96 (2.3)
Chest pain	46 (1.1)	40 (1.0)
Vascular disorders		
Hypotension	299 (7.2)	296 (7.1)

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Deep vein thrombosis	144 (3.5)	217 (5.2)
Hypertension	70 (1.7)	71 (1.7)
Thrombosis	70 (1.7)	71 (1.7)
Haematoma	58 (1.4)	66 (1.6)
Investigations		
Haemoglobin decreased	142 (3.4)	171 (4.1)
Blood creatine phosphokinase increased	102 (2.4)	104 (2.5)
Body temperature increased	85 (2.0)	88 (2.1)
Aspartate aminotransferase increased	56 (1.3)	78 (1.9)
Alanine aminotransferase increased	50 (1.2)	77 (1.8)
Gamma-glutamyltransferase increased	41 (1.0)	72 (1.7)
Nervous system disorders		
Dizziness	207 (5.0)	176 (4.2)
Headache	87 (2.1)	90 (2.2)
Somnolence	33 (0.8)	47 (1.1)
Skin and subcutaneous tissue disorders		
Pruritus	145 (3.5)	137 (3.3)
Rash	65 (1.6)	67 (1.6)
Erythema	49 (1.2)	46 (1.1)
Blister	44 (1.1)	42 (1.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	108 (2.6)	87 (2.1)
Pain in extremity	100 (2.4)	79 (1.9)
Muscle spasms	82 (2.0)	85 (2.0)
Renal and urinary disorders		
Urinary retention	184 (4.4)	169 (4.1)
Haematuria	51 (1.2)	58 (1.4)
Psychiatric disorders		
Insomnia	167 (4.0)	163 (3.9)
Anxiety	30 (0.7)	44 (1.1)
Infections and infestations		
Urinary tract infection	80 (1.9)	82 (2.0)

System Organ Classification / Preferred Term	Apixaban 2.5 mg po twice daily n (%)	Enoxaparin 40 mg sc once daily n (%)
Cardiac disorders		
Tachycardia	135 (3.2)	147 (3.5)
Bradycardia	49 (1.2)	48 (1.2)
Respiratory, thoracic and mediastinal disorders		
Cough	45 (1.1)	41 (1.0)
Dyspnoea	33 (0.8)	43 (1.0)
Blood and lymphatic system disorders		
Anaemia	110 (2.6)	131 (3.1)
Metabolism and nutrition disorders		
Hypokalaemia	50 (1.2)	52 (1.2)

Common adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of≥ 1% to < 10% (≥ 1/100 to < 1/10):

Blood and lymphatic system disorders: anaemia (including postoperative and haemorrhagic anaemia, and respective laboratory parameters)

Vascular disorders: haemorrhage (including haematoma, and vaginal and urethral haemorrhage)

Gastrointestinal disorders: nausea

Injury, poisoning and procedural complications: contusion

Uncommon adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of≥ 0.1% to < 1% (≥ 1/1,000 to < 1/100):

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 haemorrhage (including haematemesis and melaena), haematochezia

Hepatobiliary disorders: transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal), aspartate aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

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

Injury, poisoning and procedural complications: post procedural haemorrhage (including post procedural haematoma, wound haemorrhage, vessel puncture site haematoma and catheter site haemorrhage), wound secretion, incision site haemorrhage (including incision site haematoma), operative haemorrhage

Rare or very rare adverse reactions in apixaban-treated patients undergoing hip or knee replacement surgery occurring at a frequency of < 0.1% (< 1 / 1,000):

Gingival bleeding, haemoptysis, hypersensitivity, muscle haemorrhage, ocular haemorrhage (including conjunctival haemorrhage), rectal haemorrhage.

In the knee replacement surgery study during the intended treatment period, in the apixaban arm 4 cases of PE were diagnosed against no cases in the enoxaparin arm. No explanation can be given to this higher incidence of PE. In the hip replacement surgery study during the intended treatment period, in the apixaban arm 3 cases of PE were diagnosed against 5 cases in the enoxaparin arm (see CLINICAL TRIALS, Table 1).

DOSAGE AND ADMINISTRATION

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 32 to 38 days.

In patients undergoing knee replacement surgery, the recommended duration of treatment is 10 to 14 days.

The dosage of 2.5 mg taken orally twice daily and the duration specified for each type of surgery should not be exceeded.

If a dose is missed, the patient should take ELIQUIS immediately and then continue with twice daily intake as before.

ELIQUIS can be taken with or without food.

Switching treatment from parenteral anticoagulants to ELIQUIS (and vice versa) can be done at the next scheduled dose.

Anti-platelet agents other than acetylsalicylic acid should be stopped prior to surgery and restarted after surgery as recommended in the anti-platelet product information documents. For patients on acetylsalicylic acid therapy, a careful individual risk benefit assessment should be performed regarding the additional bleeding risk versus the thrombotic risk associated with the underlying diseases.

Use in Renal Impairment

No dose adjustment is necessary in patients with mild or moderate renal impairment. Limited clinical data in patients with severe renal impairment (creatinine clearance 15-29 mL/min) indicate that apixaban plasma concentrations are increased in this patient population, therefore, apixaban is to be used with caution in these patients (see PHARMACOLOGY, Pharmacokinetics). Because there is no clinical experience in patients with creatinine clearance < 15 mL/min or in patients undergoing dialysis, apixaban is contraindicated in these patients (see CONTRAINDICATIONS).

Use in Hepatic Impairment

ELIQUIS may be used with caution in patients with mild or moderate hepatic impairment (Child-Pugh A or B). No dose adjustment is required in patients with mild or moderate hepatic impairment (see PRECAUTIONS, Use in Hepatic Impairment and PHARMACOLOGY, Pharmacokinetics).

Patients with elevated liver enzymes ALT/AST > 2 x ULN or total bilirubin $\geq$ 1.5 x ULN were excluded in clinical trials. Therefore ELIQUIS should be used cautiously in this population. ALT should be measured as part of the standard pre-operative evaluation (see PRECAUTIONS, Use in Hepatic Impairment).

ELIQUIS is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including severe hepatic impairment (Child-Pugh C) (see CONTRAINDICATIONS).

Body Weight

No dose adjustment required (see PHARMACOLOGY, Pharmacokinetics).

Gender

No dose adjustment required (see PHARMACOLOGY, Pharmacokinetics).

Paediatric Use

The efficacy and safety of ELIQUIS in children below age 18 have not yet been established. No data are available.

Use in the Elderly

No dose adjustment required (see PHARMACOLOGY, Pharmacokinetics).

OVERDOSAGE

There is no antidote to ELIQUIS. Overdose of ELIQUIS may result in a higher risk of bleeding. In the event of haemorrhagic complications, the source of bleeding needs to be

investigated and appropriate symptomatic treatment initiated (see PRECAUTIONS, Haemorrhage Risk).

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 a day for 7 days or 50 mg once a day for 3 days) [10 times the daily maximum recommended human dose] had no clinically relevant adverse effects.

A nonclinical study in dogs demonstrated that oral administration of activated charcoal up to 3 hours after apixaban administration reduced apixaban exposure; therefore, activated charcoal may be considered in the management of apixaban overdose.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

ELIQUIS containing 2.5 mg apixaban for oral administration is available as yellow round, biconvex, film-coated tablets debossed with "893" on one side and "2½" on the other side in the following pack configurations:

- Cartons containing PVC/PVDC blisters of 10 film-coated tablets (1 blister of 10 film-coated tablets each), 20 film-coated tablets (2 blisters of 10 film-coated tablets each), 30 film-coated tablets (3 blisters of 10 film-coated tablets each) or 60 film-coated tablets (6 blisters of 10 film-coated tablets each).
- Cartons containing PVC/PVDC perforated unit dose blisters of 60 film-coated tablets (6 blisters of 10 film-coated tablets each) or 100 film-coated tablets (10 blisters of 10 film-coated tablets each).

Not all pack sizes and container types may be marketed.

Store below 30°C. This medicine does not require any special storage condition.

NAME AND ADDRESS OF THE SPONSOR

Bristol-Myers Squibb Australia Pty. Ltd.
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556 Princes Highway
Noble Park
Victoria 3174
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ALSO DISTRIBUTED BY:
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ABN 50 008 422 348
38-42 Wharf Road
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NSW 2114
Australia

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

21 July 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #