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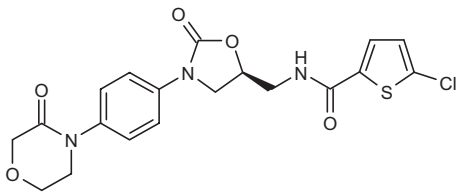
Rivaroxaban

Prop INN

Factor Xa Inhibitor
Anticoagulant

Bay-59-7939

5-Chloro-*N*-[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5(*S*)-ylmethyl]thiophene-2-carboxamide



$C_{19}H_{18}ClN_3O_5S$
Mol wt: 435.8821

CAS: 366789-02-8

EN: 307796

Abstract

Regulation of excessive coagulation through inhibition of activated serine proteases has proven to be a successful strategy for the prevention of thrombotic complications. Unfractionated heparin (UH) and low-molecular-weight heparins (LMWHs) bind to antithrombin III (ATIII) and accelerate the ability of this enzyme to inhibit activated serine proteases, thus reducing the overall activation of the coagulation cascade. Rivaroxaban (Bay-59-7939) is an oral, direct factor Xa (FXa) inhibitor developed by Bayer which belongs to a new class of small-molecule, active site-directed FXa inhibitors. Rivaroxaban does not require plasma cofactors to exert its regulatory effect on coagulation and it does not interfere with other serine proteases. Rivaroxaban demonstrated excellent *in vivo* antithrombotic activity in preliminary studies in animal models, with maximal inhibition of FX activity approximately 3 h after oral dosing. In pharmacokinetic studies, the drug was rapidly absorbed and eliminated. *In vitro* and clinical studies suggested that drug-drug interactions are unlikely. Two major studies have evaluated the efficacy and safety of rivaroxaban in the prophylaxis of thrombosis in patients undergoing orthopedic surgery. In these studies, rivaroxaban (2.5-10 mg b.i.d.) compared favorably with enoxaparin (40 mg once daily).

Synthesis

Rivaroxaban can be synthesized by two related methods:

1) Condensation of 3-morpholinone (I) with 4-fluoronitrobenzene (II) in the presence of NaH in *N*-methylpyrrolidone gives *N*-(*p*-nitrophenyl)morpholinone (III), which is reduced to aniline (IV) by catalytic hydrogenation over Pd/C in hot THF in an autoclave (1-3). Subsequent coupling of aniline (IV) with (*S*)-2-(phthalimidomethyl)oxirane (V) produces the aminoalcohol adduct (VI), which cyclizes to the oxazolidinone (VII) upon treatment with carbonyldiimidazole. After deprotection of the *N*-phthaloyl group in (VII) by means of methylamine in aqueous EtOH, the resulting primary amine (VIII) is acylated by 5-chlorothiophene-2-carbonyl chloride (IX) to furnish the target thiophene carboxamide (1-4). Scheme 1.

2) In an alternative method, acid chloride (IX), prepared by treatment of 5-chlorothiophene-2-carboxylic acid (X) with $SOCl_2$, is coupled with (*S*)-3-amino-1,2-propanediol hydrochloride (XI) in the presence of $NaHCO_3$ in 2-methyltetrahydrofuran (MTHF) to furnish the dihydroxy amide (XII). The primary alcohol function in (XII) is then brominated by means of a solution of HBr in AcOH to produce the bromohydrin (XIII), which is condensed with the morpholinoaniline derivative (IV) in the presence of collidine to yield adduct (XIV). Finally, cyclization of amino alcohol (XIV) with 1,1'-carbonyldiimidazole (CDI) in hot NMP/toluene gives the target imidazolinone compound (5). Scheme 2.

Background

Thrombotic complications are a major public health concern since they are associated with a high incidence of major disability and are a leading cause of morbidity

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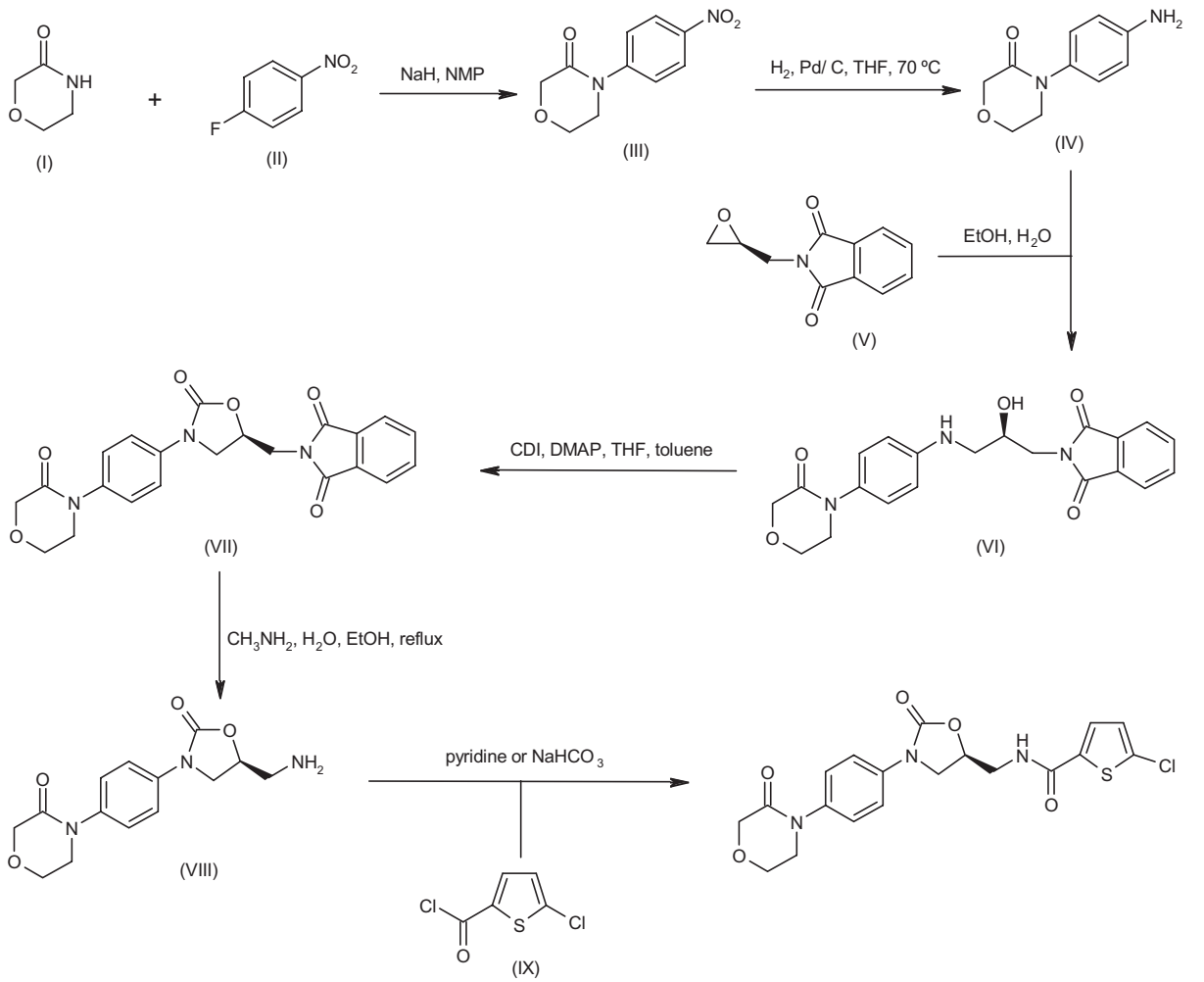
Scheme 1: Synthesis of Rivaroxaban

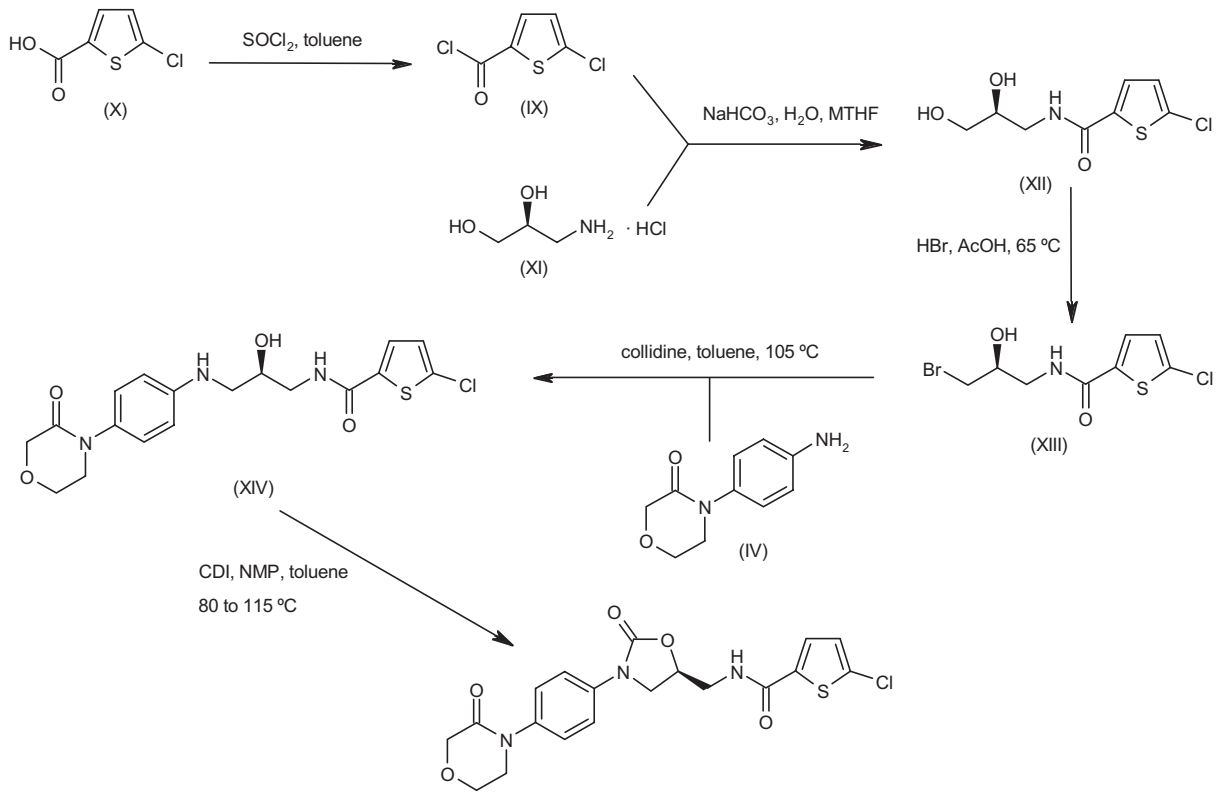


and mortality in the general population. A recent report at the 2005 American Society of Hematology (ASH) meeting assessed the global impact of venous thromboembolism (VTE) in the U.S. population (6). The study estimated more than 900,000 total VTE events, two-thirds of which were acquired in hospital; more than 600,000 of those were nonfatal VTE events and nearly 300,000 were fatal VTEs (including more than 2,200 cases of deep venous thrombosis [DVT] and 294,000 cases of pulmonary embolism [PE]). Of the deaths, the majority (93%) were due to sudden fatal PE or followed undiagnosed VTE; nearly 340,000 patients developed complications of VTE, including 336,000 with post-thrombotic syndrome (PTS) and 3,300 with chronic thromboembolic pulmonary hypertension. These data are basically in accordance with those reported for the European population (7) and suggest that universal safe and effective prophylaxis could significantly reduce the incidence of VTE and related mortality (8, 9).

According to classic concepts, coagulation mechanisms are activated through intrinsic or extrinsic pathways (10, 11). The intrinsic pathway is initiated when blood contacts surfaces other than the physiological endothelial layer. The extrinsic pathway is triggered when vascular injury leads to exposure of tissue factor (TF). In both cases, the initial activation leads to a series of enzymatic reactions in which inactive coagulation factors (mainly serine proteases) become active and capable of activating other inactive factors. The two pathways converge at the activation of factor X to Xa. Factor Xa (FXa) has a role in the further activation of factor VII to VIIa. FXa hydrolyzes and activates prothrombin (factor II) to thrombin (factor IIa). Thrombin can then further activate factors XI, VIII and V, amplifying the cascade. Ultimately the role of thrombin is to convert fibrinogen to fibrin.

Conventional anticoagulant therapies, such as oral antivitamin K, unfractionated heparin (UH) and low-molecular-weight heparins (LMWHs), exert their pharmacological action by indirect thrombin inhibition (12). Unfortunately, anticoagulant strategies have inconveniences, limitations and inherent side effects. Oral anticoagulation based on antivitamin K agents is effective,

Scheme 2: Synthesis of Rivaroxaban



although major drawbacks include the need for monitoring due to their narrow therapeutic window and large inter- and intraindividual variability in dose-response, a slow onset and offset of action, and extensive food and drug interactions (13). Individuals exposed to heparins may develop antibodies that dramatically complicate the underlying thrombotic disease, its treatment and prognosis (14, 15).

FXa has emerged as a particularly promising target for effective anticoagulation because it acts at the convergence point of the intrinsic and extrinsic coagulation pathways (Fig. 1) (16). FXa catalyzes the conversion of prothrombin to thrombin; one molecule of FXa results in the generation of thousands of thrombin molecules. Inhibiting FXa may block this burst of thrombin generation, thereby diminishing thrombin-mediated activation of coagulation and platelets.

Rivaroxaban (Bay-59-7939) is a representative of a new series of antithrombotic agents that have been developed in an attempt to circumvent some of the problems associated with conventional therapies.

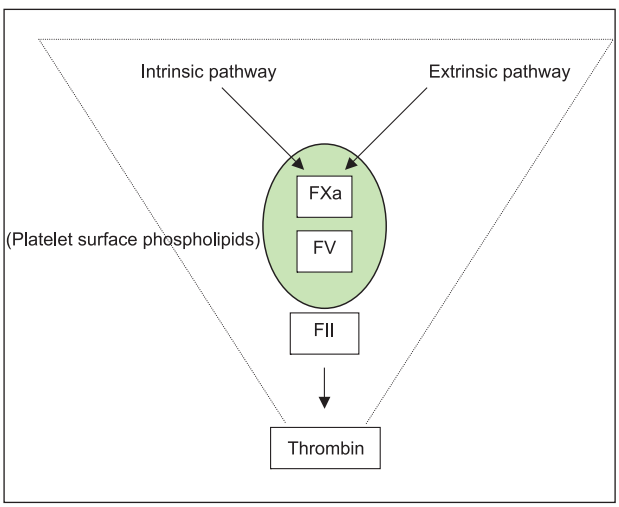


Fig. 1. Coagulation mechanisms (extrinsic and intrinsic pathways converging on FXa).

Preclinical Pharmacology

Lead optimization of a series of oxazolidinone derivatives led to the discovery of rivaroxaban (3). Basic screening tests for this compound demonstrated a highly potent and selective, direct inhibitory action on FXa (IC_{50} = 0.7 nM; K_i = 0.4 nM), excellent *in vivo* antithrombotic activity and a good pharmacokinetic profile in preliminary studies in animal models. The lipophilic chloro-

thiophene moiety in rivaroxaban is responsible for a decrease in unbound fraction and improved aqueous solubility (8 mg/l) (17), with excellent properties for an oral formulation.

The inhibitory effect of rivaroxaban was very selective on FXa. This compound did not affect related serine proteases (such as thrombin, trypsin, plasmin, FVIIa, FIXa, FXIa, urokinase and activated protein C) at concentrations up to 20 μM, demonstrating > 10,000-fold higher selectivity for FXa than for these other serine proteases. In rat plasma, rivaroxaban at 0.30-0.49 μM doubled the prothrombin time (PT). Lower concentrations (0.23 μM) caused similar prolongations of PT in human plasma. In the arteriovenous (AV) shunt model in anesthetized rats, rivaroxaban reduced thrombus weight in a dose-dependent manner, with ED_{50} values of 1 mg/kg i.v. and 5 mg/kg p.o. (18).

The X-ray crystal structure of rivaroxaban in complex with human FXa, obtained at a resolution of 2.08 Å, clarified the binding mode and the stringent requirements for high affinity observed within the oxazolidinone series investigated by Roehrig (3). Supported by two hydrogen bonds to Gly219, the oxazolidinone ring serves as a central core for directing the morpholinone residue into the S4 pocket and the chlorothiophene moiety into the S1 pocket. The key interaction of rivaroxaban with FXa in the S1 pocket involves the chlorothiophene moiety: its chlorine substituent interacts with the aromatic ring of Tyr228 located at the bottom of the S1 pocket.

The pharmacological actions of rivaroxaban have been described in more detail by Perzborn *et al.* (13). Rivaroxaban competitively inhibits human FXa (K_i = 0.4 nM) and prothrombinase activity (IC_{50} = 2.1 nM). It inhibits endogenous FXa more potently in human and rabbit plasma (IC_{50} = 21 nM) than in rat plasma (IC_{50} = 290 nM). Rivaroxaban demonstrated anticoagulant effects in human plasma, doubling the PT and activated partial thromboplastin time (aPTT) at 0.23 and 0.69 μM, respectively. *In vivo*, rivaroxaban reduced venous thrombosis (fibrin-rich, platelet-poor thrombi) dose-dependently (ED_{50} = 0.1 mg/kg i.v.) in a rat venous stasis model. The compound reduced arterial thrombus formation in AV shunt models in rats (ED_{50} = 5.0 mg/kg p.o.) and rabbits (ED_{50} = 0.6 mg/kg p.o.). Slight inhibition of FXa (32% at ED_{50}) reduced thrombus formation in the venous model; to affect arterial thrombosis in the rat and rabbit models, stronger inhibition of FXa (74% and 92%, respectively, at ED_{50}) was required. In rabbits, the ED_{50} was 14-fold lower than in the rat AV shunt model, consistent with the 14-fold lower IC_{50} for FXa inhibition in rabbit compared with rat plasma. Administration of rivaroxaban did not significantly affect bleeding times in rats and rabbits at antithrombotic doses in the AV shunt model (3 mg/kg p.o.).

The effects of rivaroxaban were additionally investigated (19) in plasma-based assays such as PT, aPTT, HepTest, thrombin time (TT) and Russell's viper venom (RVV) time. Rivaroxaban had a concentration-dependent anticoagulant effect in all tests except the TT, demonstrating selective inhibition of both the intrinsic and extrinsic coagulation pathways. A modified method utilizing diluted fibrinogen-deficient plasma with thromboplastin (extrinsic activator) and ellagic acid (intrinsic activator) was used to investigate the relative effects of rivaroxaban on FXa and thrombin generation. Rivaroxaban strongly inhibited FXa and thrombin generation in the extrinsic pathway activation studies, with IC_{50} values of 0.06 and 0.12 μg/ml, respectively. In the intrinsic system, the IC_{50} values were 0.19 and 0.14 μg/ml, respectively. Rivaroxaban also had anticoagulant effects in native normal human blood, as measured by the activated clotting time and thromboelastographic methods. It inhibited the generation of prothrombin fragments F1+2 (IC_{50} = 7.1 μg/ml), fibrinopeptide A (IC_{50} = 5.1 μg/ml) and thrombin-antithrombin complex (IC_{50} = 4.9 μg/ml), but it did not appear to affect agonist-induced platelet aggregation (epinephrine, ADP, collagen, arachidonic acid) at concentrations up to 10 μg/ml.

Rivaroxaban inhibits clot-bound FXa in experimental models at therapeutic concentrations (20). Current LMWHs are not very effective against clot-bound thrombin. Inhibition of clot-bound FXa, as well as free FXa, may increase the efficacy of antithrombotic drugs. The effects of rivaroxaban on clot-bound factor Xa activity were investigated in comparative studies with fondaparinux on *in vitro* clots produced around polystyrene hooks in normal platelet-poor plasma. Clots were incubated for 1 h at 37 °C in plasma deficient in fibrinogen and FX and containing increasing amounts of rivaroxaban or fondaparinux (0-15,000 nM final concentration). Prothrombin activation was monitored by measuring F1+2 fragments. Fondaparinux inhibited clot-bound FXa, with results consistent with those previously reported for this anticoagulant. Rivaroxaban inhibited clot-bound FXa concentration-dependently (IC_{50} = 75 nM), with almost complete inhibition (85-97%) obtained at concentrations > 500 nM.

The anticoagulant properties of rivaroxaban have been studied in comparison to fondaparinux and enoxaparin (21). Rivaroxaban strongly inhibited both human and bovine FXa (IC_{50} = 0.3-0.6 μg/ml), independently of ATIII. Rivaroxaban prolonged PT, aPTT, HepTest and RVV time at concentrations < 0.62 μg/ml, independently of ATIII. Thus, the compound directly inhibits both intrinsic and extrinsic coagulation pathways. Neither fondaparinux nor enoxaparin exerted any anti-FXa effects in ATIII-depleted systems, and showed weaker inhibitory effects compared to rivaroxaban in the presence of ATIII. Rivaroxaban inhibited thrombin generation and FXa activity at concentrations of 0.5-1.0 μg/ml in the ATIII-depleted system using both extrinsic and intrinsic activators, but neither fondaparinux nor enoxaparin had any measurable effect up to 10 μg/ml. Supplementing ATIII partially restored the effects of fondaparinux and enoxaparin. It was concluded from these studies that rivaroxaban does not require plasma cofactors (ATIII) to exert its anticoagulant action on FXa. Additional tests demonstrated that it did not show cross-reactivity in heparin-induced thrombocytopenic (HIT serum) screening, compared to fondaparinux and enoxaparin (12% and 66%, respectively).

Pharmacokinetics and Metabolism

The metabolism and distribution of rivaroxaban were investigated after administration of single intraduodenal (bile duct-cannulated rats) and oral (dogs, humans) doses of [^{14}C]-labeled drug (22). The major compound in plasma was unchanged drug at all time points and across all species. In total, approximately 95%, 78% and 89% of the dose administered could be attributed to unchanged drug and its metabolites in rats, dogs and humans, respectively. No major circulating metabolites were detected in plasma. Urinary excretion of radioactivity was 17%, 52% and 66% of the dose in rats, dogs and humans, respectively, and fecal/biliary excretion of radioactivity was 81%, 43% and 28% of the dose, respectively. The urinary and fecal/biliary radioactivity profiles were similar in rats, dogs and humans, with metabolites arising from two major metabolic pathways, *i.e.*, oxidative degradation of the morpholino moiety (which leads to metabolite M-1 via cleavage of the ring) and hydrolysis of the amide bond (with subsequent conjugation of the 5-chloro-2-thiophenecarboxylic acid with glycine to metabolite M-4). Metabolite M-1, the main metabolite, was eliminated via the renal and fecal/biliary routes, whereas metabolite M-4 was excreted renally.

In studies *in vitro* (23), incubation of rivaroxaban with liver microsomes from different species, including man, and with rat and human hepatocytes in sandwich culture, revealed that the morpholino moiety was the main target of oxidative metabolism; subsequently, cleavage of the morpholino moiety was observed. A second biotransformation pathway, cleavage of the amide bond and subsequent conjugation of the 5-chloro-2-thiophenecarboxylic acid with glycine, was detected. Cytochrome P-450 CYP3A4 is the key enzyme for phase I biotransformation in humans. However, the high K_m values for formation of the primary metabolites in human liver microsomes indicate a low affinity of rivaroxaban for CYP3A4, suggesting a moderate susceptibility for drug-drug interactions only with strong CYP3A4 inhibitors. This was further demonstrated *in vitro* in interaction studies with various CYP3A4 substrates and inhibitors. Rivaroxaban exhibited neither inductive nor inhibitory potential towards major human CYP isoforms.

The pharmacokinetics of rivaroxaban were initially investigated in rats and dogs (17). The compound was rapidly absorbed after oral dosing, with an absolute bioavailability of 57-66% in rats and 60-86% in dogs. Plasma pharmacokinetics of rivaroxaban were linear across the investigated dose range (1-10 mg/kg in rats, 0.3-3 mg/kg in dogs). Plasma clearance was low: 0.4 l/kg/h in rats and 0.3 l/kg/h in dogs; volume of distribution (V_{ss}) was moderate: 0.3 l/kg in rats and 0.4 l/kg in dogs. The elimination half-life after oral administration was short in both species (0.9-2.3 h). Whole-body autoradiography showed moderate tissue affinity. No retention or small volume enrichments of rivaroxaban-related radioactivity were observed. The plasma protein binding of rivaroxaban was high, species-dependent and fully reversible. Rivaroxaban was rapidly excreted in rats and dogs, and was not irreversibly retained. A dual mode of excretion (biliary/fecal and renal) was observed.

The pharmacokinetics of single doses were studied in a single-center, randomized, single-blind, placebo-controlled, dose-escalation study in 108 healthy white male subjects aged 19-45 years (16). Subjects received single oral doses of either rivaroxaban (1.25-80 mg) or placebo; in addition, one group received two doses of rivaroxaban (5-mg tablet and oral solution) or placebo in a crossover design. After administration of oral tablets containing 5-80 mg, peak plasma concentrations were reached around 2 h, with a median t_{max} of 112 min for 5 mg and of 120 min for 80 mg (Tables I and II). The area under the plasma concentration-time curve (AUC) values ranged from 446 to 3298 μg.h/l. Peak plasma concentrations (C_{max}) ranged from 72 μg/l for 5-mg tablets to 316 μg/l for 80-mg tablets. At doses above 10 mg, increases in peak plasma concentrations and AUC were less than dose-proportional. A benefit of the decreased bioavailability of the highest doses of rivaroxaban may be a reduced risk of unintentional overdosing. The terminal

Table I: Pharmacokinetics of rivaroxaban following administration of single doses (tablets) to healthy volunteers (16).

Parameter	5 mg (n=6)	10 mg (n=8)	20 mg (n=7)	40 mg (n=8)	80 mg (n=6)
AUC (μg.h/l)	446	1020	1612	2412	3298
AUC_{norm} (g.h/l)	7479	8766	6369	5128	3286
C_{max} (μg/l)	72	141	173	234	316
$C_{max,norm}$ (g/l)	1208	1211	684	498	315
$t_{1/2}$ (h)	4.27	9.07	7.60	8.88	17.40
V_z/f (l/kg)	0.82	1.49	1.72	2.50	7.66
CL/f (l/h)	11.2	9.8	12.4	16.6	24.3
Ae_{ur} (%)	—	—	—	19.8*	10.9†
t_{max}‡ (h)	1.88	2.00	1.50	1.50	2.00

Data are given as geometric mean values, unless otherwise indicated. Data are not shown for 15-, 30- and 60-mg tablets. AUC, area under plasma concentration-time curve; C_{max}, peak plasma concentration; $t_{1/2}$, terminal half-life; t_{max}, time to peak plasma concentration; AUC_{norm}, area under concentration-time curve divided by dose per kilogram of body weight; $C_{max,norm}$, maximum drug concentration in plasma divided by dose per kilogram of body weight; V_z/f, apparent volume of distribution during terminal phase after oral administration; CL/f, total plasma clearance calculated after oral administration (apparent oral clearance); Ae_{ur}, amount of drug excreted in urine. *Mean ± SD, 0-48-h sampling interval. †Mean ± SD, 0-72-h sampling interval. ‡Median.

Table II: Pharmacokinetics of rivaroxaban following administration of multiple doses to healthy volunteers (24).

Parameter	5 mg o.d. (n=7)	5 mg b.i.d. (n=7)	5 mg t.i.d. (n=6)	10 mg b.i.d. (n=7)	20 mg b.i.d. (n=7)	30 mg b.i.d. (n=7)
AUC_{τ} (μg.h/l)	505.5	458.5	557.3	863.8 (18.6)	1,903.0	2,728.0
C_{max} (μg/l)	76.4	85.3	123.8	158.0 (18.8)	318.1	451.9
$t_{1/2}$ (h)	8.4	7.0	5.8	7.6 (26.7)	8.0	9.2
t_{max} (h)	3.00	3.00	2.00	2.98	2.50	3.02

Values are geometric means, accept t_{max} (median). See Table I for definitions.

half-lives ($t_{1/2}$) ranged from 4.2 to 17.4 h. Urinalysis for unchanged compound showed that approximately 40% of the administered dose was excreted renally in unchanged form after administration of a dose of 1.25 mg. However, at doses of 60 and 80 mg, only approximately 10% of the administered dose was present in urine as the parent drug. In this study, maximum inhibition of FXa activity occurred 1-4 h after administration of tablets. The half-life of the biological effect was 6-7 h. FXa activities had not completely returned to baseline at 24 h for doses above 5 mg. Rivaroxaban selectively inhibited FXa activity; thrombin (FIIa) and antithrombin were unaffected. Inhibition of FXa activity and prolongation of PT correlated well with plasma concentrations (r = 0.949 and 0.935, respectively). PT prolongation followed a similar profile to inhibition of FXa activity and may be used for monitoring the anticoagulant action of rivaroxaban if necessary.

The pharmacokinetics after oral administration of multiple doses using several dosing regimens (5 mg once, twice [b.i.d.] or 3 times daily [t.i.d.], and 10, 20 or 30 mg b.i.d. for 7 days) were examined in healthy male subjects (age: 20-45 years, body mass index: 18.6-31.4 kg/m^2) (24). Studies were sequentially performed on days 0 and 3-7. Steady state was reached at day 7. Exposure to rivaroxaban in terms of AUC and C_{max} was dose-proportional for all doses (5, 10, 20 and 30 mg b.i.d.) after day 0 and day 7. Maximum plasma concentrations of rivaroxaban were reached (t_{max}) approximately 3-4 h after initial administration for all doses and all regimens. C_{max} reached 85.3, 123.8, 158 and 318 μg/l with doses of 5 mg b.i.d., 5 mg t.i.d., 10 mg b.i.d. and 20 mg b.i.d. respectively. The $t_{1/2}$ after day 0 was 3.7-5.8 h, which was prolonged on day 7 to 5.8-9.2 h. There was no relevant accumulation at any dose. Maximum inhibition of FXa activity occurred approximately 3 h after dosing. With oral doses of 5 mg once daily, b.i.d. and t.i.d., maximum inhibition of FXa activity on day 0 was similar and there were no relevant differences in maximum inhibition of FXa activity on day 7 compared with day 0 for the three regimens. FXa activity was inhibited for up to 12 h after 5 mg once daily and beyond 24 h after b.i.d. and t.i.d. dosing in some subjects. PT and aPTT were prolonged in a dose-dependent manner on day 7.

The influence of food on rivaroxaban pharmacokinetics was investigated in one study (25). In the presence of food, t_{max} was delayed by 1.25 h; C_{max} and AUC were increased, with reduced interindividual variability at higher doses of rivaroxaban. Compared with baseline, rivaroxaban resulted in a relative maximum PT prolongation of 44% (10 mg) and 53% (20 mg) in the fasted state, compared with 53% and 83%, respectively, after food.

Currently, agents used for the prevention of VTE require dose adjustments for patients in extreme weight categories. A single-center, randomized, single-blind, placebo-controlled, parallel-group study tested the influence of extremely low and high body weight on the safety, tolerability, pharmacodynamics and pharmacokinetics of a single 10-mg dose of rivaroxaban administered with food (26). In total, 48 healthy male and female subjects aged 20-54 years and in three different weight groups (50 kg or less, 70-80 kg and > 120 kg) were evaluated; 12 received placebo and 36 received the drug. The bioavailability of rivaroxaban in terms of AUC was similar in all three weight groups (p = 0.205). However, C_{max} was 24% higher in subjects with a body weight of 50 kg or less compared with normal-weight subjects. For subjects weighing > 120 kg, C_{max} was similar to normal-weight subjects. No pharmacokinetic differences between men and women were detected in the normal-weight and 120 kg groups. FXa was inhibited by rivaroxaban in all three groups, with a maximum inhibition (E_{max}) of 46.8%, 45.8% and 41.7%, respectively, in subjects weighing 50 kg or less, 70-80 kg and > 120 kg, maximum inhibition being observed about 2-3 h after administration. AUC for inhibition of FXa activity was comparable for all groups regardless of body weight. The clotting tests aPTT and HepTest were also distinctly prolonged after drug administration in all weight groups; the prolongation was slightly more pronounced in subjects weighing 50 kg or less than in the other weight groups.

Overall, rivaroxaban was well tolerated in the above-mentioned studies. No serious adverse events were reported. Events of mild to moderate intensity were infrequent and resolved after discontinuation of the drug.

Clinical Studies

Two major studies have evaluated the efficacy and safety of rivaroxaban in the prophylaxis of thrombosis in patients undergoing orthopedic surgery (27, 28).

A multicenter, parallel-group, double-blind, double-dummy study evaluated the efficacy and safety of rivaroxaban in the prevention of thrombosis in 621 patients undergoing elective total knee replacement (27). Patients were randomly assigned to oral rivaroxaban (2.5, 5, 10, 20 and 30 mg b.i.d., initiated 6-8 h postsurgery) or s.c. enoxaparin (30 mg b.i.d., initiated 12-24 h postsurgery). Treatment was continued until bilateral venography was performed 5-9 days after surgery. The primary efficacy endpoint was a composite of any DVT (proximal and/or distal), confirmed nonfatal PE and all-cause mortality during treatment. Of the 613 patients treated, 366 (59.7%)

were evaluable for the primary efficacy analysis. The primary efficacy endpoint occurred in 31.7%, 40.4%, 23.3%, 35.1% and 25.4% of patients receiving 2.5, 5, 10, 20 and 30 mg b.i.d. doses of rivaroxaban, respectively (test for trend, $p = 0.29$), compared with 44.3% in the enoxaparin group. With regard to safety, the primary endpoint of the study was major postoperative bleeding during treatment. The incidence of major postoperative bleeding events was 1.0%, 0%, 1.9%, 3.1% and 7.5%, respectively, for rivaroxaban doses of 2.5, 5, 10, 20 and 30 mg b.i.d. A statistically significant dose trend was observed with increasing doses of rivaroxaban ($p = 0.0007$). Major postoperative bleeding occurred in 1.9% of patients in the enoxaparin group. There was no significant difference in the incidence of major postoperative bleeding between any of the rivaroxaban dose groups and enoxaparin. The incidence of clinically relevant nonmajor bleeding and minor bleeding showed a similar pattern to the primary endpoint, with a lower incidence in the rivaroxaban 2.5-10 mg b.i.d. groups. Similarly, the composite of major postoperative bleeding or clinically relevant nonmajor bleeding was lower in the rivaroxaban 2.5-10 mg b.i.d. groups. No significant difference was observed compared with enoxaparin. Mean transfusion volumes were lowest in patients receiving rivaroxaban 2.5 mg b.i.d. (149 ml) and highest in the 30 mg b.i.d. group (230 ml). Mild increases in the liver enzymes aspartate transaminase (AST) and alanine transaminase (ALT) were observed in all treatment groups, with no dose-response relationship observed in the rivaroxaban groups. There were no cases of clinically relevant thrombocytopenia. The incidence of nausea and vomiting with early postoperative administration of rivaroxaban was low in all groups. Rivaroxaban did not have untoward effects on ECG parameters.

A double-blind, double-dummy, dose-ranging study evaluated the efficacy and safety of rivaroxaban in comparison with enoxaparin in patients undergoing elective total hip replacement (28). A total of 706 patients were randomized to oral rivaroxaban (2.5, 5, 10, 20 or 30 mg b.i.d.), starting 6-8 h after surgery, or s.c. enoxaparin 40 mg once daily, starting on the evening before surgery. Treatment was continued until mandatory bilateral venography was performed 5-9 days after surgery. Of 706 patients treated, 548 were eligible for the primary efficacy analysis. The primary efficacy endpoint was the incidence of any DVT, nonfatal PE and all-cause mortality; rates were 15%, 14%, 12%, 18% and 7%, respectively, for rivaroxaban 2.5, 5, 10, 20 and 30 mg b.i.d., compared with 17% for enoxaparin. No significant trend in dose-response relationship was observed for rivaroxaban. As in the previous study, the primary safety endpoint was major postoperative bleeding. Major postoperative bleeding was observed in 0.8%, 2.2%, 2.3%, 4.5% and 5.4% of patients receiving rivaroxaban doses of 2.5, 5, 10, 20 and 30 mg b.i.d., respectively, compared with 1.5% for enoxaparin. There was a significant dose trend for major postoperative bleeding ($p = 0.045$), as shown by logistic regression. There were no significant differences in the incidence of major postoperative bleeding between any rivaroxaban dose and enoxaparin. No fatal bleeding or bleeding into a critical organ was reported, and most major bleeding events were confined to the surgical site. Overall, the observed mean transfusion volumes were lowest in patients receiving rivaroxaban 2.5 and 5 mg b.i.d. Fewer patients in the rivaroxaban 2.5, 5 and 10 mg b.i.d. groups experienced serious treatment-emergent adverse events (7.6%, 8.8% and 10.5%, respectively) compared to enoxaparin (11.4%); serious treatment-emergent adverse events were observed in more patients in the rivaroxaban 20 and 30 mg b.i.d. groups (14.9% and 16.2%, respectively), mainly because of major postoperative bleeding events. Rivaroxaban did not have untoward effects on ECG parameters or substance-specific effects on laboratory parameters, including liver enzymes (ALT or AST), that were statistically different from those observed in the group of patients receiving enoxaparin.

In summary, rivaroxaban appears to exhibit a good efficacy and safety profile which is comparable to other established anticoagulants. Phase III development is currently under way for the prevention of VTE after surgical intervention (29, 30) and phase III clinical trials are also planned for the prevention of stroke in patients with atrial fibrillation and for the treatment of VTE (31).

Drug Interactions

Possible concomitant treatments in patients receiving anticoagulants for either the prevention or treatment of VTE may include medications such as heparins, nonsteroidal antiinflammatory drugs (NSAIDs), aspirin or other antiplatelet agents. The potential interactions of rivaroxaban with representative drugs from these groups have been explored at the pharmacokinetic and pharmacodynamic level (32-36).

Bridging therapy may be necessary when a patient receiving oral anticoagulation requires parenteral anticoagulants, or *vice versa*. The potential interaction and feasibility of bridging therapy using rivaroxaban and enoxaparin or heparin was investigated in a rat AV shunt model (32). Co-administration of rivaroxaban and enoxaparin resulted in an additive effect: thrombus formation was inhibited by 65% ($p < 0.05$ *vs.* enoxaparin alone; $p < 0.01$ *vs.* rivaroxaban alone). Rivaroxaban in combination with heparin significantly reduced thrombus formation (49%) compared with rivaroxaban alone (25%; $p < 0.02$) or heparin alone (27%; $p < 0.02$), demonstrating an additive effect. aPTT was significantly increased after co-administration of rivaroxaban and enoxaparin compared with enoxaparin alone ($p < 0.05$) or rivaroxaban alone ($p < 0.005$). aPTT was increased > 13-fold with heparin alone; this was not affected by the addition of rivaroxaban. The prolongation of PT achieved with rivaroxaban alone was not affected by the addition of heparin. Enoxaparin and heparin almost completely inhibited FXa; this effect was not reduced by the addition of rivaroxaban. In conclusion, rivaroxaban did not reduce the antithrombotic efficacy of enoxaparin or heparin, and *vice versa*. These studies in animals suggest that rivaroxaban and

enoxaparin or heparin may be used sequentially, if necessary, for bridging therapy.

A randomized, two-way crossover study investigated the influence of naproxen 500 mg on the safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban in 11 healthy male subjects (33). The AUC and C_{max} for rivaroxaban both increased by approximately 10% following co-administration of naproxen; however, this small increase in rivaroxaban bioavailability was not considered clinically relevant. Rivaroxaban, naproxen and the combination were well tolerated. Adverse events were reported by 3 subjects and all were mild in intensity; there were no drug-related, treatment-emergent adverse events. Rivaroxaban significantly inhibited FXa activity by 35% and prolonged PT by 1.4 times compared to baseline, aPTT by 1.3 times compared to baseline and HepTest by 1.9 times compared to baseline, with no influence for naproxen. No interaction was observed with respect to collagen-stimulated platelet aggregation. The study concluded that there were no relevant interactions between rivaroxaban and naproxen, although some individuals may be more sensitive to combination of these drugs.

Another randomized, two-way crossover study evaluated the influence of aspirin on the safety, tolerability, pharmacodynamics and pharmacokinetics of rivaroxaban in 13 healthy male subjects, with an aspirin run-in period (34). Treatments were: A, 500 mg aspirin on day 1 and 100 mg aspirin on day 2; B, 15 mg rivaroxaban; or C, a combination of A and B (with rivaroxaban administered on day 2). Concomitant administration of aspirin did not influence the pharmacokinetics of rivaroxaban (AUC = 1156 μg.h/l [coefficient of variation (CV) = 30.62] and 1053 μg.h/l [CV = 22.58]; C_{max} = 126.3 μg/l [CV = 30.01] and 133.4 μg/l [CV = 26.44] for rivaroxaban and combination, respectively). Rivaroxaban significantly inhibited FXa activity by 32%, prolonged PT by 1.3 times compared to baseline, aPTT by 1.3 times compared to baseline and HepTest by 1.7 times compared to baseline, with no influence for aspirin. Rivaroxaban did not alter maximum collagen-activated platelet aggregation, indicating no difference between aspirin alone and the combined treatment. Although the combination of rivaroxaban with aspirin significantly increased bleeding time, this difference was small compared with aspirin alone. In conclusion, there was no relevant interaction between rivaroxaban and aspirin at the doses tested.

The possible additive effects of rivaroxaban, aspirin (5 mg/kg p.o.), clopidogrel (2.5 mg/kg p.o.) or abciximab (250 μg/kg) on agonist-induced platelet aggregation in platelet-rich plasma (PRP) were investigated in primates (35). Blood samples were collected prior to the administration of aspirin, clopidogrel or abciximab, then 2 h after the administration of aspirin or clopidogrel, or 10 min after abciximab. The effect of rivaroxaban was studied in PRP by *ex vivo* supplementation (0-10 μg/ml). In addition, platelet activation by TF was investigated by flow cytometry measuring P-selectin expression in citrated whole blood taken from primates treated with aspirin, clopidogrel or abciximab. Rivaroxaban (10 μg/ml or less) in PRP did not significantly affect agonist-induced aggregation (arachidonic acid, TRAP, ADP, collagen, thrombin). *Ex vivo* supplementation with rivaroxaban in PRP from primates did not modify the inhibition of agonist-induced aggregation by aspirin, clopidogrel or abciximab. In whole blood, *ex vivo* supplementation with rivaroxaban produced concentration-dependent inhibition of TF-mediated P-selectin expression. These studies suggest that the drug has no effect on agonist-induced aggregation (arachidonic acid, TRAP, ADP, collagen, thrombin) and does not affect the antiplatelet effect of aspirin, clopidogrel or abciximab. However, rivaroxaban decreased platelet activation by TF indirectly via inhibition of thrombin generation, and may thereby affect thrombin-induced aggregation *in vivo*.

Patients who have been exposed to heparins may develop antibodies that cause heparin induced thrombocytopenia (HIT). One study evaluated whether rivaroxaban cross-reacts with HIT antibodies, in order to examine its potential as an alternative anticoagulant for the management of patients with HIT (36). The effect of rivaroxaban on platelet activation mediated by HIT antibodies was examined in sera collected from 63 patients diagnosed with HIT (HIT sera), using platelet aggregation assays, the [^{14}C]-5-HT release assay and flow cytometry for the detection of platelet P-selectin expression and platelet microparticle formation. Conventional heparin and enoxaparin were used for comparison. As expected, heparin strongly activated platelets and caused their aggregation, and gave a positive response with 100% of the HIT sera tested. Enoxaparin showed positive responses with 73% of the sera. Rivaroxaban did not activate platelets or cause aggregation with any of the HIT sera tested, confirming that there is no interaction between rivaroxaban and HIT antibodies.

Data from a recent study indicate that co-administration with antacids (aluminium magnesium hydroxide or ranitidine) does not modify pharmacokinetic parameters of rivaroxaban. No significant differences in C_{max} and AUC were observed with co-administration of rivaroxaban and ranitidine or the antacid (24).

Sources

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