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MONOGRAPH

OTAMIXABAN

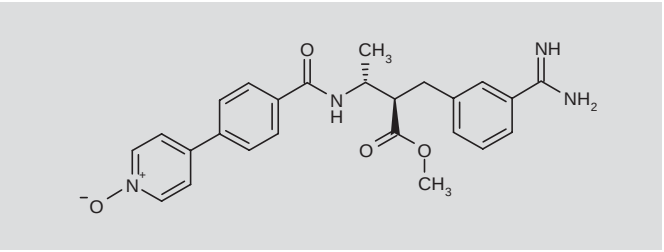
Rec INN

Coagulation Factor Xa Inhibitor
Treatment of Acute Coronary Syndrome

FXV-673
XRP-0673

2(*R*)-(3-Amidinobenzyl)-3(*R*)-[4-(1-oxidopyridin-4-yl)benzamido]butyric acid methyl ester

InChI: 1S/C25H26N4O4/c1-16(22(25(31)33-2)15-17-4-3-5-21(14-17)23(26)27)28-24(30)20-8-6-18(7-9-20)19-10-12-29(32)13-11-19/h3-14,16,22H,15H2,1-2H3,(H3,26,27)(H,28,30)/t16-,22-/m1/s1



$C_{25}H_{26}N_4O_4$
Mol wt: 446.4983
CAS: 193153-04-7
EN: 295864

SUMMARY

Although the treatment of acute coronary syndromes (ACS) has improved tremendously in recent decades, treatment continues to evolve in order to increase efficacy, personalize therapy and minimize the risk of bleeding. Current antithrombotic therapies for patients with non-S-T segment elevation myocardial infarction (NSTEMI) and unstable angina are effective but limited by the need for monitoring, indirect or incomplete activity against aspects of the coagulation cascade and the risk of bleeding. Some anticoagulants act on activated factor X (FXa), a serine protease that plays an essential role in clot formation through its involvement in the conversion of prothrombin to thrombin. A great deal of activity has been devoted to the development of direct FXa inhibitors. One result of these efforts has been the synthesis of otamixaban, which is characterized by a rapid onset of action, a short half-life and inhibition of fluid-phase and clot-bound FXa. In clinical trials, otamixaban has demonstrated relevant pharmacodynamic activity without an increased risk of major or minor bleeding in patients undergoing nonurgent percutaneous coronary intervention compared to unfractionated heparin (UFH), and in patients with non-S-T elevation acute coronary syndromes, significant reductions in events without an increase in major or minor bleeding compared to UFH. A phase III trial is currently under way.

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SYNTHESIS

The cycloaddition reaction between 4-vinylpyridine (I) and methyl coumalate (II) in hot mesitylene in the presence of Pd/C gives the methyl pyridylbenzoate (III), which is hydrolyzed with NaOH in H_2O/MeOH/THF and the resulting carboxylic acid (IV) is converted to the acid chloride (V) upon refluxing with $SOCl_2$ (1-3). Acylation of the amino ester (VI) using either pyridylbenzoic acid (IV) by means of TBTU and NMM in DMF (4) or acid chloride (V) in the presence of Et_3N in EtOH (1-3) affords amide (VII), which is then oxidized at the pyridine nitrogen with *m*-chloroperbenzoic acid (1-3) or magnesium monoperoxyphthalate (4) in CH_2Cl_2 to provide the corresponding *N*-oxide (VIII). Finally, nitrile (VIII) is submitted to Pinner reaction with HCl in cold MeOH to afford imidate (IX), followed by heating with methanolic ammonia (1-4). Scheme 1.

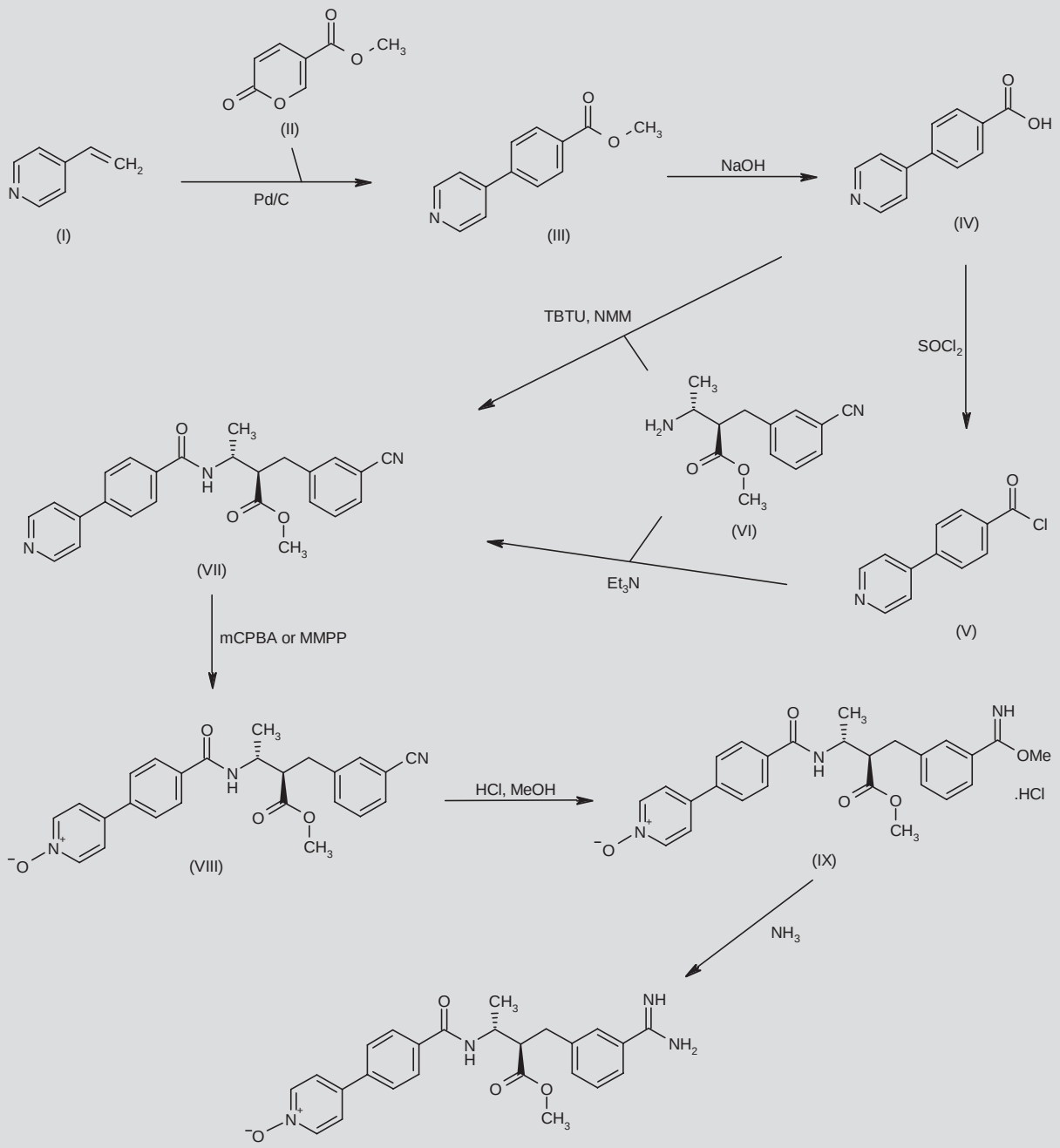
Amino ester (VI) can be prepared by the following methods:

Protection of methyl 3(*R*)-aminobutyrate (X) by treatment with either di-*tert*-butyl dicarbonate by means of DMAP and Et_3N or benzyl chloroformate and $NaHCO_3$ in CH_2Cl_2 produces the respective *tert*-butyl and benzyl carbamates (XIa) and (XIb), which by diastereoselective alkylation of the lithium enolates generated from the corresponding amino esters and LHMDS with 3-cyanobenzyl bromide (XII) yields 2(*R*)-(3-cyanobenzyl)butyric acid esters (XIIIa) and (XIIIb), which are finally deprotected by either treatment with trifluoroacetic acid in CH_2Cl_2 or catalytic hydrogenolysis in the presence of Pd/C in EtOH (VI) (1, 2). Alternatively, the synthesis of amino ester (VI) has been reported by direct alkylation of the lithium enolate of methyl 3(*R*)-aminobutyrate (X) with 3-cyanobenzyl bromide (XII) in cold THF (4). Scheme 2.

BACKGROUND

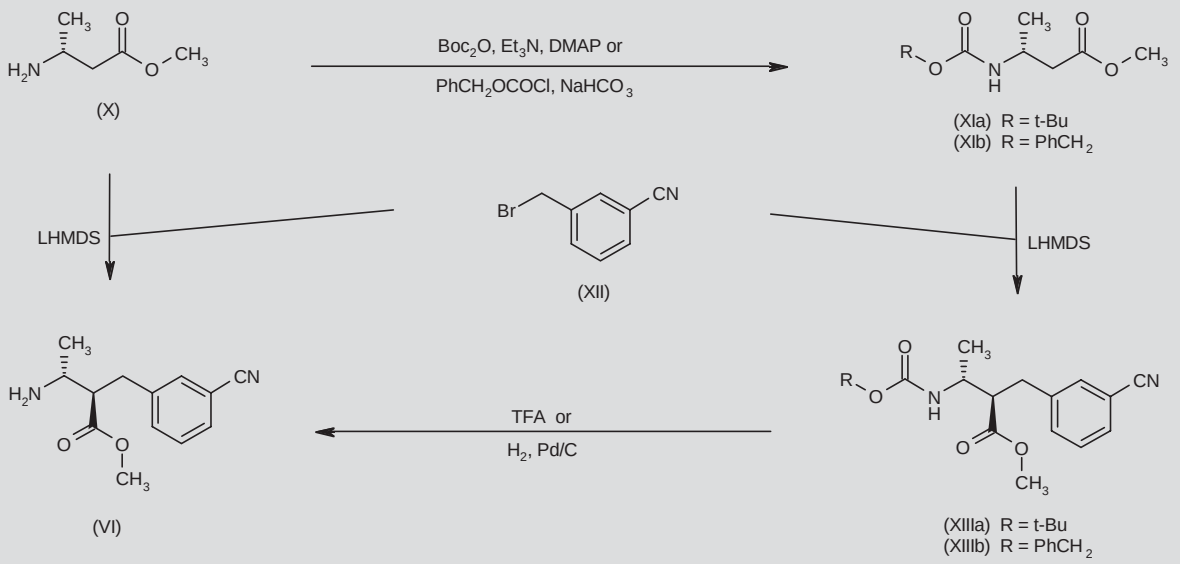
Acute coronary syndromes (ACS) are among the most common and life-threatening disorders affecting individuals. Fortunately, in

Scheme 1. Synthesis of Otamixaban



recent decades ACS have proven amenable to multiple therapeutic strategies, and to the application of more than one of these at the same time. ACS result from reduced myocardial perfusion due to coronary artery disease (CAD), with the cause often being rupture or disruption of an atherosclerotic plaque, leading to activation of platelets and the coagulation cascade, resulting in turn in thrombus formation. The resulting ACS are a spectrum of conditions including unstable angina, non-S-T segment elevation myocardial infarction (NSTEMI) and S-T segment elevation myocardial infarction (STEMI). In patients presenting with chest pain, pain in other areas such as

Scheme 2. Synthesis of Amino Ester (VI)



the arms or jaw, nausea, vomiting, dyspnea, diaphoresis and lightheadedness, STEMI is differentiated from unstable angina and NSTEMI by 12-lead electrocardiogram findings, while unstable angina is differentiated from NSTEMI by the measurement of a cardiac biomarker in serum, with a cardiac-specific troponin being the preferred biomarker. Elevated troponin is indicative of myocardial damage and NSTEMI.

Anticoagulant pharmacotherapy forms part of a complex management strategy for patients presenting with the signs of an ACS. The strategy is based on the presence or absence of S-T segment elevation, patient characteristics, risk factors for ischemic events, risk of bleeding complications from treatments, patient and physician preferences, whether an early conservative or invasive management strategy is chosen, whether the treatment is before diagnostic angiography or afterwards, or after hospital release, and whether a stent was implanted or not, and if so, what kind (5, 6).

While treatment is best when tailored to a patient's risk of ischemic cardiac events and treatment-related complications, STEMI is generally treated with reperfusion by thrombolysis or percutaneous coronary intervention (PCI), with post-myocardial infarction treatment consisting of dual antiplatelet therapy (aspirin and clopidogrel), a β-blocker, a statin and an angiotensin-converting enzyme (ACE) inhibitor. Patients diagnosed with non-S-T segment elevation ACS (NSTEMI and unstable angina) receive antiplatelet (aspirin and clopidogrel, and possibly a glycoprotein gpIIb/IIIa receptor antagonist) and anticoagulant treatment (unfractionated or low-molecular-weight heparin [LMWH]), along with antianginal therapy, statin therapy and, in NSTEMI patients, ACE inhibitor therapy. PCI is considered for patients with high-risk features (7).

Physicians practicing through the latter half of the twentieth century and into the current one will have seen tremendous advances in outcomes for ACS patients, resulting in part from the advent of PCI, the introduction of risk stratification algorithms, the discovery of biomarkers of myocardial necrosis and the introduction of newer treatments, leading for example to the use of LMWH (enoxaparin) in place of unfractionated heparin as anticoagulant therapy. However, residual morbidity and mortality are high among patients with non-S-T segment elevation ACS. Data from the Global Registry of Acute Coronary Events (GRACE) showed a high rate of aspirin and ADP receptor antagonist use in non-S-T segment elevation ACS patients in 2005, as well as an increase compared to 1999 in the use of PCI in these patients, although in-hospital and 6-month mortality rates were 2.2% and 3.3%, respectively. Six-month rates of recurrent myocardial infarction and stroke were 2.9% and 0.7%, respectively. This is due to several potential factors. Antiplatelet treatments such as aspirin and clopidogrel each block only one of many platelet activation pathways, and do not affect the activity of thrombin. Patient responses to antiplatelet therapy also vary. Therapy with gpIIb/IIIa receptor antagonists such as eptifibatide, tirofiban and abciximab has demonstrated efficacy but may be limited by safety issues such as increased bleeding. Long-term treatment with antithrombin agents is not always given, lipid-lowering treatments do not completely prevent the generation or progression of atherosclerotic lesions, and revascularization procedures do not address the underlying thrombosis (8).

Currently available antithrombin agents have their limitations. Unfractionated heparin (UFH) inhibits thrombin and activated factor X (FXa) through binding with antithrombin III. Long a standard treatment, UFH has pharmacodynamic activity which is unpre-

dictable and requires monitoring, and can induce thrombocytopenia. Compared with UFH, LMWHs such as enoxaparin have the advantages of more predictable activity, a longer half-life and a lower risk of heparin-induced thrombocytopenia. LMWHs have greater FXa-inhibitory activity than UFH. The inhibitory effects of UFH and LMWH, however, are mainly on fluid-phase thrombin and FXa and not clot-bound thrombin- and clot-bound prothrombinase-associated FXa. Direct thrombin inhibitors such as hirudins, bivalirudin, argatroban, dabigatran and ximelagatran are not active against FXa and do not block thrombin generation. Indirect FXa inhibitors such as fondaparinux act against FXa but not thrombin, inhibiting thrombin generation without inhibiting thrombin activity. Fondaparinux has demonstrated efficacy in treating ACS, but it must be delivered parenterally, its activity is dependent on antithrombin III levels and it does not inhibit FXa in the prothrombinase complex, a key element in clot formation (8-10).

The improvement in outcomes seen with innovations in the treatment of ACS may also have led to acceptance of the increase in treatment-related bleeding risk, with bleeding considered a relatively simple complication to manage. But bleeding has been found to be linked to the risk of death, myocardial infarction and stroke in ACS patients, and transfusion may also negatively impact event risk. These discoveries led to the inclusion of treatment-related bleeding risk as part of the process of deciding upon an individual's treatment strategy. Current pharmacological treatments used in ACS can increase the risk of bleeding and cause problems in the event of non-minor bleeding. These treatments may need to be interrupted and neutralized, but not all antithrombin therapies have antidotes that are perfectly effective, and antiplatelet agents are irreversible inhibitors. Treatment interruption naturally increases the risk of thrombotic events (11).

Factor Xa is one of a number of serine proteases involved in the blood coagulation cascade that catalyzes the conversion of prothrombin to thrombin via the prothrombinase complex (FXa, factor Va [FVa], phospholipid and Ca^{2+}), potentiating clot formation as thrombin converts fibrinogen to insoluble fibrin (see Fig. 1). Thrombin is also a platelet activator (12, 13). One molecule of FXa is able to generate more than 1,000 molecules of thrombin, and the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to the rate catalyzed by free FXa, causing a burst of thrombin generation (9).

Inhibition of FXa in patients with ACS is expected to have fewer effects on hemostasis compared to heparin, direct thrombin inhibitors and gpIIb/IIIa receptor antagonists, as FXa occupies the penultimate position in the coagulation system with respect to thrombin; this may result in a reduced risk of bleeding (14). Direct FXa inhibition may prove superior to indirect inhibitors due to inhibition of both free and prothrombinase-bound FXa, predictable pharmacokinetic and pharmacodynamic profiles, leading to decreased bleeding risk and reducing the need for frequent monitoring, and the possibility of oral administration (10).

In 1994 an extensive screening effort was undertaken to identify direct FXa inhibitors as antithrombotic agents but failed to discover a viable lead compound. The effort then shifted to investigation of β-lactam-based FXa inhibitors; after lead structure identification, structure–activity relationship analysis and optimization yielded otamixaban, which was found to be a potent, selective, rapid-acting, competitive and reversible inhibitor of FXa. Otamixaban was selected for further evaluation (12).

The selectivity of FXa inhibition by otamixaban enables it to inhibit thrombin generation rather than thrombin activity. The agent can inhibit both fluid-phase and clot-bound FXa, potentially inhibiting further thrombus propagation in addition to inhibiting thrombin generation. Its reversibility, with a rapid onset of action and a short half-life, make it appropriate for ACS treatment. Otamixaban is mainly cleared unchanged via the biliary system, indicating that dose modification will not be necessary in the case of renal insufficiency. The drug can prolong the activated partial thromboplastin time (aPTT), but monitoring of aPTT does not appear to be necessary since there is a strong correlation between otamixaban's anti-Xa pharmacodynamic effect and its blood concentration, and only small interpatient pharmacokinetic variability (9, 13). Otamixaban has been evaluated in two large clinical trials, the SEPIA-PCI and SEPIA-ACS1/TIMI-42 studies. SEPIA-PCI included patients undergoing nonurgent PCI in whom otamixaban was associated with reductions in prothrombin fragments 1+2 and dose-related increases in anti-FXa. The difference in TIMI (Thrombolysis In Myocardial Infarction) major or minor bleeding between otamixaban and UFH was also not significant in this study (15). In the SEPIA-ACS1/TIMI-42 trial in patients with non-S-T segment elevation ACS, otamixaban doses effectively preventing events were not associated with significantly higher rates of TIMI major or minor bleeding compared to unfractionated heparin (UFH) (13). A phase III trial comparing otamixaban and UFH plus eptifibatide in patients with unstable angina/non-S-T segment elevation ACS scheduled to undergo an early invasive strategy is presently recruiting patients (16).

PRECLINICAL PHARMACOLOGY

As part of an effort to target FXa for antithrombotic effects, researchers at Aventis synthesized a β-aminoester class of FXa inhibitors. Structure–activity relationship analyses and optimization led to otamixaban, with a K_i value of 0.4 nM for FXa compared to > 4000 nM for thrombin (FIIa) and 301 nM for trypsin. Selectivity against the related serine proteases FIIa, activated protein C (APC), plasmin, trypsin and tissue-type plasminogen activator (tPA) was greatly improved over earlier inhibitors. Otamixaban was also found to inhibit coagulation of human plasma in vitro, with aPTT doubled at a concentration of 0.41 μM. In a rat model of ferrous chloride-induced arterial thrombosis, otamixaban was associated with a dose-dependent increase in time to occlusion. The maximal effective dose was approximately 50 μg/kg by bolus and 5 μg/kg/min by i.v. maintenance infusion, which was associated with a 40% reduction in thrombus mass compared to control. Antithrombotic activity was also seen in an acute canine model of arterial and venous electrolyte injury (3).

Further pharmacological characterization of otamixaban revealed potent inhibition of human FXa (K_i = 0.52 nM) in enzyme assays using chromogenic substrates, with selectivity against other proteases of > 1,000-fold, except for trypsin, against which selectivity was approximately 600-fold. Otamixaban proved to be a fast, tight-binding and reversible inhibitor of FXa. FXa converts prothrombin to thrombin through the prothrombinase complex and the effect of

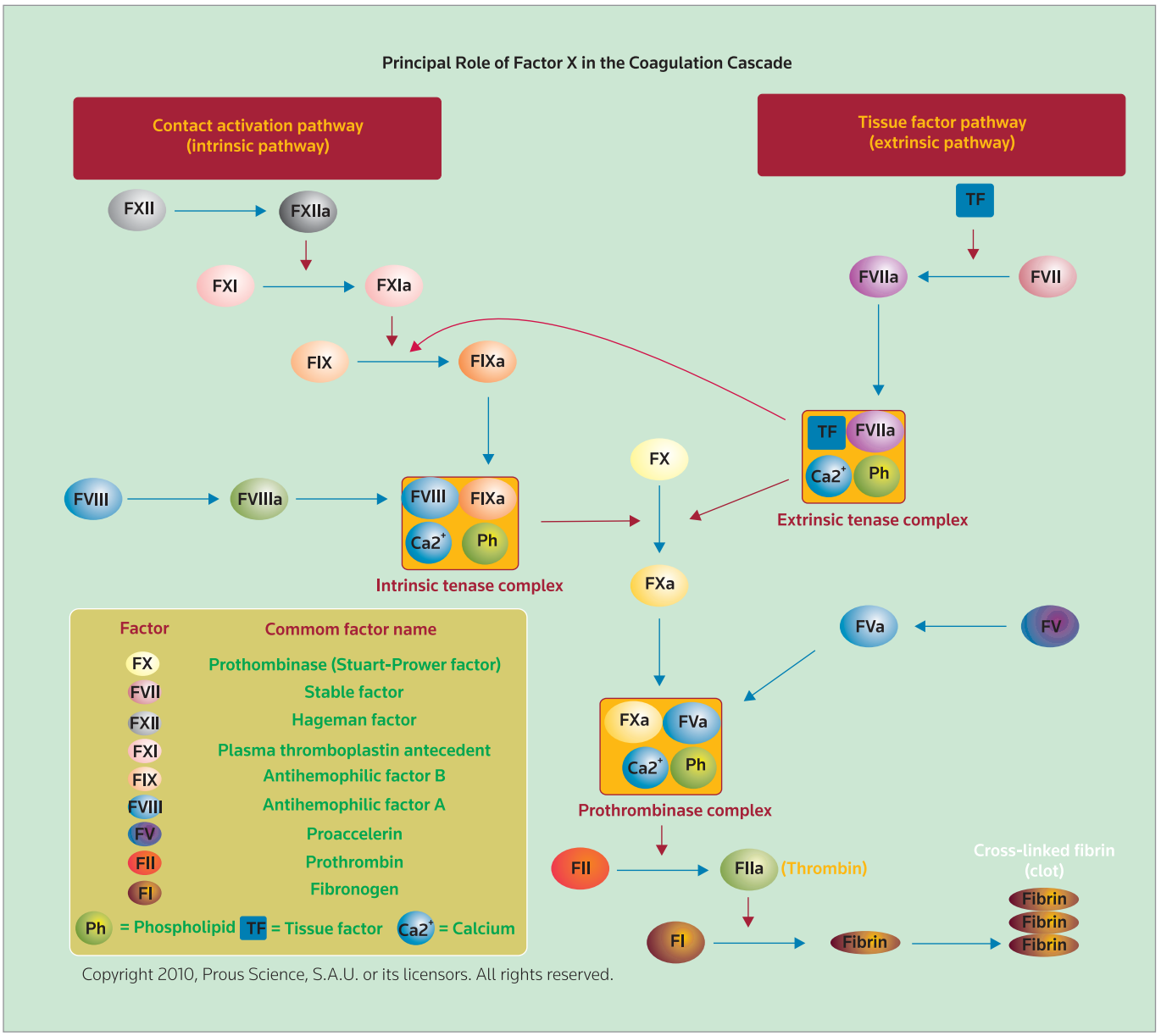


Figure 1. Under normal conditions, the extrinsic blood coagulation pathway is activated in the wake of injury when the potent procoagulant tissue factor (TF) is summoned to the site of injury, where it binds to factor VII (FVII), which is subsequently converted to activated factor VII (FVIIa). The TF/FVIIa complex activates factor X (FX), and FXa binds to FVa on the cell surface. The FXa/FVa complex facilitates the conversion of prothrombin (FII) to the active form of thrombin (FIIa), leading to the formation of a stable fibrin clot. In the intrinsic pathway, activated factor XII (FXIIa) activates factor XI (FXI), which in turn activates factor IX (FIX). The TF/FVIIa complex also activates factor IX. The small amount of thrombin generated locally activates factor VIII (FVIII) and platelets, and the complex formed by FVIIIa and FIXa activates FX on the surface of activated platelets. Again, FXa in association with FVa catalyzes the conversion of prothrombin to thrombin, leading to clot formation.

otamixaban on prothrombinase-bound FXa was assessed using liposomes or fresh platelets as phospholipid sources. Otamixaban concentration-dependently inhibited thrombin generation with IC_{50} values of 1.38 and 2.55 nM, respectively, for prothrombinase-bound FXa on liposomes and platelets. Concentration-dependent inhibition was also seen when otamixaban was added after the initiation of thrombin generation. Otamixaban concentration-dependently prolonged aPTT and prothrombin time (PT) and had no effect on platelet aggregation in the platelet-rich plasma (PRP) system. In electrolytic-injured canine arterial and venous thrombosis models, otamixaban significantly and dose-dependently prolonged time to vessel occlusion and reduced thrombus formation in the carotid artery and jugular vein. Doses associated with maximal antithrombotic effects were not associated with systemic hypocoagulability

(PT and aPTT), suggesting a reduced bleeding risk with effective doses (9).

Experiments were conducted in vitro to compare the effects of otamixaban, the LMWH enoxaparin and the direct thrombin inhibitor melagatran on thrombin generation in human plasma and PRP. Thrombin activity against a fluorogenic substrate was measured using tissue factor as a trigger. Otamixaban potently and concentration-dependently inhibited thrombin generation in plasma and PRP, with efficacy similar to the comparator agents (17).

Adjunctive treatment with otamixaban was compared to heparin and the platelet gpIIb/IIIa receptor antagonist RPR-109891 in a canine model of recombinant tissue plasminogen activator (rt-PA)-induced coronary thrombolysis. Thrombus formation was induced by electrolytic injury to stenosed coronary artery, and one of the i.v. treatments was administered along with aspirin and rt-PA (100 µg/kg bolus + 20 µg/kg/min for 60 min) 15 min after the start of drug infusion. All eight animals given the high dose of otamixaban (100 µg/kg bolus + 10 µg/kg/min for 135 min) had reperfusion compared to four of eight given heparin (60 U/kg bolus + 0.7 U/kg/min for 135 min) and five of eight given RPR-109891 (30 µg/kg bolus + 0.45 µg/kg/min for 135 min). Reocclusion occurred in two of eight vessels in the high-dose otamixaban group, while all vessels in the heparin and RPR-109891 groups reoccluded. Blood flow was higher with otamixaban, which dose-dependently enhanced vessel patency. The high dose of otamixaban was associated with a 60% reduction in thrombus mass compared to vehicle and heparin treatment. This dose of otamixaban prolonged aPTT by a maximum of 2.8-fold and PT by 1.9-fold compared to 2.7- and 1.2-fold, respectively, with heparin. Template bleeding time was increased 2.8-fold by the high dose of otamixaban, 1.7-fold with heparin and 4-fold with RPR-109891, and with otamixaban the increase returned to baseline after the end of the infusion. Otamixaban did not significantly inhibit ex vivo thrombin-induced platelet aggregation, unlike the other two treatments (14).

Arterial wall passivation –wherein antithrombotic treatment renders the vessel nonreactive to thrombogenic forces even in the presence of wall injury– was assessed with otamixaban in conscious dogs undergoing electrolytic injury to induce carotid artery thrombosis. Sedated and anesthetized dogs underwent electrolytic injury with a 100-µA anodal current applied to the stenosed carotid artery over 1 h on day 1 while simultaneously receiving otamixaban (100 µg/kg + 10 µg/kg/min), heparin (60 U/kg + 0.7 U/kg/min) or vehicle administered i.v. for 3 h. The process was repeated on day 2, with a 200-µA anodal current applied for 3 h and drug treatment again given for 3 h. While blood flow declined in the heparin group in a manner similar to the vehicle group during the injury phases, the incidence of vessel occlusion was reduced from 100% with vehicle to 28% with heparin at 3 h on day 2. Otamixaban administration, however, was associated with a sustained and nonoscillatory blood flow during the injury phases and none of the vessels became occluded. Carotid artery blood flow was higher in the otamixaban group compared to the other groups during and after the infusions, and the recovery of blood flow on days 3, 4 and 5 was superior with otamixaban compared to heparin. Thrombus masses, assessed on day 5, were 87% and 70% less, respectively, compared to the placebo and heparin groups ($P < 0.05$). Template bleeding test times were shorter on day 5 with the active agents compared to vehicle (18).

In a model of recurrent platelet thrombosis in anesthetized, open-chest pigs, injury and stenosis of the coronary artery were associated with cyclical reductions in blood flow. At an otamixaban dose of 15 µg/kg + 1.5 µg/kg/min, blood flow reductions were abolished in six of seven pigs. A dose of 5 µg/kg + 0.5 µg/kg/min abolished blood flow reductions in all four pigs treated, while a dose of 1 µg/kg + 0.1 µg/kg/min was ineffective. Bleeding time, assessed by puncture of a small ear vein with a hypodermic needle, was not significantly prolonged with otamixaban compared to baseline. The highest dose prolonged aPTT and activated clotting time, while the middle and lower doses prolonged PT. The thrombin inhibitor bivalirudin was able to abolish reductions in blood flow at doses of 250 µg/kg + 25 µg/kg/min and 500 µg/kg + 50 µg/kg/min, but these doses were associated with significantly prolonged bleeding times. Unlike otamixaban, bivalirudin also significantly inhibited thrombin-induced platelet aggregation (19).

PHARMACOKINETICS AND METABOLISM

Various studies of the pharmacokinetics and pharmacodynamics of otamixaban have been conducted in healthy volunteers and patients.

Healthy male volunteers were enrolled in two double-blind, placebo-controlled phase I studies in which they received escalating doses of otamixaban as 6-h infusions with and without bolus infusions, or 24-h infusions. Assessment of pharmacokinetics showed increased otamixaban exposure with dose (more than dose-proportionally) with low intersubject variability, rapid plasma distribution and elimination, excretion in urine (25% of the dose) and in bile (75% of the dose), with renal clearance remaining constant and a 30% decrease in clearance and volume of distribution over the dose range. The drug rapidly disappeared from the blood upon cessation of administration, declining 46-67% in the first half hour, a potentially important effect in the event of bleeding or adverse events. A two-compartment pharmacokinetic model accounted for the 30% decrease in plasma clearance and volume of distribution and was used to predict otamixaban bolus plus 3-h infusion doses for phase II and III clinical studies. Otamixaban was also well tolerated in these subjects over a dose range of 1.7-183 µg/kg/min, with no relevant changes in laboratory values or vital signs (20). Data from three phase I/II studies were also fitted simultaneously to a two-compartment model accommodating the change in plasma clearance and volume of distribution with dose, and pharmacokinetic/pharmacodynamic simulations were used to predict doses for a dose-ranging phase II study with target plasma concentrations at end of infusion (C_{eoi}) of 75-600 ng/mL. Combined bolus + 3-h infusions allowed target C_{eoi} to be reached immediately with a dip not exceeding 20% of C_{eoi} (21).

Data from healthy male volunteers enrolled in one of two dose-escalation phase I studies were used in mixed-effects modeling to determine the correlation between otamixaban plasma concentrations and anticoagulant effects. The concentration–effect relationships over time for aPTT, PT, dilute PT (dPT), Heptest clotting time (HCT) and Russel's viper venom-induced clotting time (RVVT) did not show evidence of hysteresis. Pharmacokinetic/pharmacodynamic rela-

tionships for aPTT, PT, dPT and RVVT were linear, while the relationship for HCT followed a sigmoidal E_{max} model. The pharmacokinetic/pharmacodynamic response (slope) and their corresponding interindividual variability (s/ng/mL [% coefficient of variation (CV)]) were 0.263 (29.1%) for RVVT, 0.117 (10.1%) for dPT, 0.058 (19.3%) for aPTT and 0.021 (11.4%) for PT. The parameter estimates for HCT with their corresponding interindividual variability (%CV) were 71 ng/mL (30.0%) for EC_{50} and 186 s (63.7%) for E_{max}. The model's predictions for plasma concentrations required for doubling of clotting time were similar to observed values (22).

The effects of gender and age on pharmacokinetic and pharmacodynamic measures were evaluated in a study in which healthy subjects received otamixaban 0.5 mg/kg as a 6-h i.v. infusion. Pharmacokinetics were similar in young and elderly males and females, with a trend towards reduced clearance and steady-state volume of distribution in the elderly. Neither gender nor age affected aPTT, PT, RVVT or HCT (23).

The effects of hepatic and renal impairment on the pharmacokinetics, pharmacodynamics and tolerability of otamixaban are being investigated in two phase I clinical studies. A study in subjects with mild to moderate hepatic impairment is expected to enroll 24 subjects and to end by May 2011, while a study in subjects with severe renal impairment is to enroll 16 subjects and also to end in May 2011 (24, 25).

SAFETY

Safety data from two large phase II studies are available. No difference between TIMI major or minor bleeding was seen between patients undergoing nonurgent PCI given otamixaban or UFH in the SEPIA-PCI Trial (Study to Evaluate the Pharmacodynamics, the Safety and Tolerability, and the Pharmacokinetics of Several Intravenous Regimens of the Factor Xa Inhibitor Otamixaban [XRP0673], in Comparison to Intravenous Unfractionated Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention). In the randomized, double-blind, placebo-controlled study, i.v. bolus + 3-h infusion regimens of otamixaban were 0.025 mg/kg + 0.035 mg/kg/h, 0.045 mg/kg + 0.065 mg/kg/h, 0.080 mg/kg + 0.120 mg/kg/h, 0.120 mg/kg + 0.160 mg/kg/h and 0.140 mg/kg + 0.200 mg/kg/h. Otamixaban and UFH (i.v. bolus of 50-70 U/kg) were given within 20 min of PCI. There were 947 patients enrolled. TIMI major or minor bleeding occurred in 2.8% of the pooled otamixaban groups and in 3.8% of patients given UFH; there were no significant differences between any otamixaban group and the UFH group. Almost all bleeding events were TIMI minimal bleeds and most occurred at the vascular access site, while only four were TIMI major (two in otamixaban-treated patients). Ischemic events through day 30 occurred in 5.8%, 7.1%, 3.8%, 2.5% and 5.1%, respectively, of the increasing otamixaban dose groups and in 5.6% of the UFH group; the differences between otamixaban dose groups and UFH were not significant. There were no deaths through day 30 (15).

In the phase II SEPIA-ACS1/TIMI-42 study in 3,241 patients with NSTEMI ACS, the rate of the primary safety endpoint, TIMI major or minor bleeding unrelated to coronary artery bypass graft, was dose-related with otamixaban. In SEPIA-ACS1/TIMI-42, patients set to undergo invasive treatment were randomized within 24 h of presentation to double-blind treatment with otamixaban, with a 0.08 mg/kg bolus followed by infusions of 0.035-0.175 mg/kg/h, or UFH (60 IU/kg i.v. bolus followed by infusion of 12 IU/kg/h) plus eptifibatide (180 µg/kg i.v. bolus followed by infusion of 1.0-2.0 µg/kg/min). Primary safety endpoint rates with the lowest doses were below that seen with UFH, but these doses were not considered effective. With the 0.105 and 0.140 mg/kg/h doses, rates were not significantly higher than that in the UFH arm: 3.1%, 3.4% and 2.7%, respectively. The rate with the highest dose (5.4%) was significantly increased compared to UFH. Minimal bleeding rates were similar with UFH and the two lower doses of otamixaban but were increased by 2-fold with the 0.105 and 0.140 mg/kg/h doses and increased by nearly 3-fold with the 0.175 mg/kg/h dose (13, 26).

CLINICAL STUDIES

The safety, pharmacokinetics and pharmacodynamics of otamixaban were investigated in stable coronary artery disease patients (N = 119) enrolled in a randomized, double-blind, multicenter, placebo-controlled study. Otamixaban was given as a 1-min bolus at doses of 15, 30, 45 and 60 µg/kg followed by continuous 24-h infusion of 50, 100, 125 and 150 µg/kg/h, respectively. As was seen in healthy volunteers, plasma otamixaban concentrations increased more than dose-proportionally and 30 min after cessation of the infusion otamixaban plasma concentrations were half of the C_{eoi} values. Mild renal impairment, a characteristic of half of the patients enrolled, had no clear effect on total systemic clearance. Anticoagulant and FXa-inhibitory activities were seen at 3 min after the start of treatment, with effects differing by dose. aPTT, RVVT, dPT and international normalized ratio (INR) followed the time course of otamixaban plasma concentrations and of anti-FXa activity and returned to baseline approximately 6 h after the end of infusion. At the highest otamixaban dose, the fold changes from baseline were 4.4 for RVVT (1.15 for placebo), 3.15 for dPT (0.98 for placebo), 2.11 for aPTT (0.94 for placebo) and 1.70 for INR (0.94 for placebo). No evidence of interactions with concomitant medications was seen and there were no deaths or serious adverse events (AEs) or AEs leading to study discontinuation. There were also no major or minor bleeding events. Insignificant bleeding events, mostly consisting of laboratory measures, occurred in 23% of the placebo group and 35%, 65%, 75% and 79%, respectively, of the increasing otamixaban dose groups. No safety signals arose in vital signs, electrocardiography or clinical laboratory values (27).

Data from this study were used to develop a population pharmacokinetic/pharmacodynamic model. A three-compartment model accounting for the decrease in clearance and volume of distribution with increasing doses (without a change in half-life) and pharmacodynamic data were added sequentially to the validated model. This allowed prediction of bolus + 4-h infusion otamixaban doses needed to achieve mean otamixaban concentrations of 50-600 ng/mL and corresponding changes in anti-FXa activity and aPTT for phase II/III studies (28).

In the above-mentioned SEPIA-PCI Trial, 947 patients undergoing nonurgent PCI were randomized to receive i.v. bolus + 3-h infusion regimens of otamixaban or UFH within 20 min of PCI for the prevention of coronary artery thrombosis due to arterial injury. Otamixaban was given as an i.v. bolus followed by a 3-h infusion (0.025 mg/kg + 0.035 mg/kg/h, 0.045 mg/kg + 0.065 mg/kg/h, 0.080 mg/kg +

0.120 mg/kg/h, 0.120 mg/kg + 0.160 mg/kg/h or 0.140 mg/kg + 0.200 mg/kg/h). UFH was administered as an i.v. bolus at 50-70 U/kg. The primary endpoints were change in prothrombin fragments 1+2 (F1+2) and anti-FXa activity. Significant variability in F1+2 may have limited its utility as a surrogate marker of activity, and no otamixaban dose–response relationship was seen for this outcome. The highest otamixaban dose was, however, associated with a greater reduction in F1+2 than UFH. Anti-FXa levels were 65, 155, 393, 571 and 691 ng/mL, respectively, with increasing otamixaban doses, a significant dose–response relationship. Thrombus was noted during PCI in 1.0% of the pooled otamixaban groups (8 patients) and in 1.3% of UFH-treated patients (2 patients). PCI was successful in 97% of the pooled otamixaban groups and in 92% of the UFH group (15).

SEPIA-PCI set the stage for the multicenter phase II SEPIA-ACS1/TIMI-42 study, which included 3,241 patients with NSTEMI ACS and found certain doses of otamixaban to provide substantially more protection from events compared to UFH. In the randomized, double-blind trial, patients were treated within 24 h of presentation to otamixaban with a bolus of 0.08 mg/kg followed by infusions of 0.035, 0.070, 0.105, 0.140 or 0.175 mg/kg/h, or UFH (60 IU/kg i.v. bolus followed by infusion of 12 IU/kg/h) plus eptifibatide (180 µg/kg i.v. bolus followed by infusion of 1.0-2.0 µg/kg/min). While the lowest otamixaban dose studied was discontinued due to lack of activity, intermediate doses of 0.105 and 0.140 mg/kg/h significantly reduced the incidence of the primary efficacy endpoint, the composite of all-cause death, new myocardial infarction, severe recurrent ischemia requiring revascularization or bailout use of a gpIIb/IIIa inhibitor through day 7, with relative risks of 0.61 and 0.58, respectively, versus UFH. The rates in these groups were 3.8%, 3.6% and 6.2%, respectively. A reduction was seen with the 0.175 mg/kg/h otamixaban dose (4.3%), but this was not significant compared to UFH. Differences in the rates for the primary endpoint lasted over the 180 days of follow-up. The relative risks of death or myocardial infarction were 0.52 and 0.56, respectively; with the intermediate doses versus UFH these reductions largely account for the differences in the primary endpoint. The 0.035 and 0.070 mg/kg/h otamixaban doses were associated with much higher rates of bailout gpIIb/IIIa inhibitor use for recurrent ischemia or for a thrombotic complication compared to UFH. These doses were also associated with increased rates of procedural thrombotic complications compared to UFH in patients who underwent PCI. The results pointed to evaluation of otamixaban given as a 0.08 mg/kg bolus followed by infusion of 0.100-0.140 mg/kg/h in phase III studies (13, 26).

A phase III trial comparing otamixaban and UFH plus eptifibatide in patients with unstable angina/NSTEMI ACS scheduled to undergo an early invasive strategy was initiated in the spring of this year and is expected to end in June 2012. The randomized, double-blind study is to enroll 10,930 patients and has as the primary efficacy endpoint the composite of all-cause death and myocardial infarction. TIMI major and minor bleeding is the primary safety endpoint (16).

DRUG INTERACTIONS

Coadministration of otamixaban and aspirin did not affect the therapeutic effects of either agent in a randomized, double-blind, placebo-controlled, three-way crossover study in 68 healthy male volunteers. Otamixaban was administered as 6-h infusions of 0.3 and 0.5 mg/kg with and without aspirin, which was given as a 300-mg daily oral dose starting 2 days before and continued on the infusion day. Washout between treatments lasted at least 4 weeks. No pharmacokinetic interaction between otamixaban and aspirin was observed. Otamixaban dose-dependently prolonged RVVT, aPTT and dPT, effects not altered by aspirin coadministration. Aspirin did not affect these coagulation measures. Conversely, otamixaban did not affect tests of platelet plug formation (collagen–adenosine [CADP-CT] and collagen–epinephrine [CEPI-CT] closure times), and coadministration with aspirin had the same effect on these parameters as administration of aspirin alone. Otamixaban did not affect collagen- or ADP-induced platelet aggregation, while aspirin decreased the former and to a lesser extent the latter. The same effects were seen with aspirin alone and with coadministration of the agents. Assessment of skin bleeding time revealed a slight prolongation with drug coadministration, although no clinically relevant bleeding occurred. Safety data showed that 31 AEs occurred in 19 subjects, including 2 subjects who experienced mild epistaxis and mild gum bleeding which resolved without treatment. No changes in laboratory parameters were clinically relevant (29).

Otamixaban's anticoagulant effects and tirofiban's antiplatelet effects were not altered when the two agents were administered together in a study in 15 healthy male volunteers. Otamixaban pharmacokinetics were not altered in the presence of tirofiban (12).

SOURCE

sanofi-aventis (FR).

DISCLOSURES

The author states no conflicts of interest.

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