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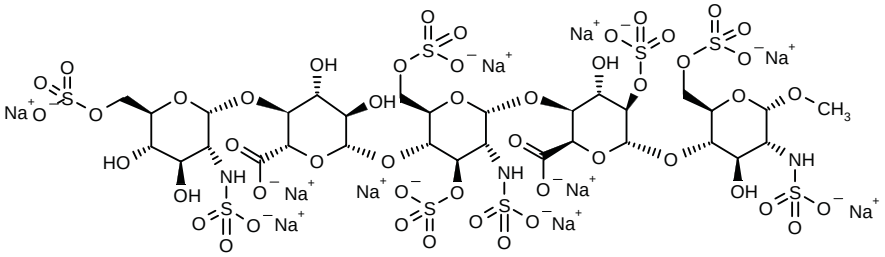
Fondaparinux Sodium

Prop INN

Anticoagulant
Factor Xa Inhibitor
Treatment and Prevention of Deep Vein Thrombosis

Org-31540
SR-90107A
Arixtra®
Quixidar®

O-[2-Deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl]-(1→4)-*O*-(β-D-glucopyranurosonyl)-(1→4)-*O*-[2-deoxy-3,6-di-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl]-(1→4)-*O*-(2-*O*-sulfo-α-L-idopyranurosonyl)-(1→4)-*O*-[2-deoxy-1-*O*-methyl-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranoside] decasodium salt



$C_{31}H_{43}N_3Na_{10}O_{49}S_8$
Mol wt: 1728.081
CAS: 114870-03-0
CAS: 104993-28-4 (as free acid)
EN: 208310

Abstract

Although a number of antithrombotics have been developed in recent years, deep venous thrombosis and arterial thrombosis are still a major cause of morbidity and mortality in developed countries, and the search for better antithrombotic agents continues. Fondaparinux is a synthetic pentasaccharide that potently and selectively inhibits factor Xa. Such compounds are expected to have advantages over thrombin inhibitors, *i.e.*, a higher safety margin and less frequent monitoring. Fondaparinux exerts concentration-dependent anticoagulant activity *in vitro* in human whole blood, while having little or no effect on prothrombin time, thrombin clotting time, activated partial thromboplastin time or platelet aggregation. Antithrombotic effects have been demonstrated in animal models of both venous and arterial thrombosis. Fondaparinux proved to be safe and effective in phase II and III clinical trials for the prevention and treatment of venous and arterial thrombosis. Further studies are under way which should help to better define its role in specific clinical indications. For now, the pentasaccharide has been approved by the FDA for use in the prophylaxis of deep vein thrombosis in patients undergoing hip fracture, hip replacement or knee replacement surgery.

Introduction

In recent years, considerable progress has been made in developing better antithombotics. However, venous thromboembolism remains an important complication of surgery. Despite the use of preventive measures, deep venous thrombosis continues to be an important cause of morbidity and mortality, and arterial thrombosis, mainly stroke and acute coronary syndromes, is the major cause of mortality in developed countries. For these reasons, the search continues for an ideal antithrombotic agent with high efficacy but without side effects.

In this search, the natural pentasaccharide fondaparinux has been developed (1-3). Fondaparinux is the

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first in a new class of antithrombotic agents which are synthetic selective inhibitors of activated factor X (factor Xa) with no components from animal sources (4). Its structure and function are related to unfractionated heparin and to low-molecular-weight heparins. Unfractionated heparin is a glycosaminoglycan that exerts its anticoagulant effect via antithrombin, a natural anticoagulant, resulting in inhibition of both thrombin and factor Xa. Low-molecular-weight heparins are formed by depolymerization of unfractionated heparin and were developed in order to reduce bleeding complications and cross-reactivity with heparin platelet factor 4 (PF4) antibodies that cause heparin-induced thrombocytopenia (5). Compared with unfractionated heparin, low-molecular-weight heparins have 2-4 times greater inhibitory activity against factor Xa than against thrombin because of their shorter chain length.

The pentasaccharide sequence was determined to be the shortest chain that can catalyze the antithrombin-mediated inhibition of factor Xa while having no antithrombin action. The original pentasaccharide sequence was identified from natural heparin by fractionation procedures (6). A specific pentasaccharide was then prepared by an innovative process of glycosaminoglycan synthesis (7, 8). Subsequently, the α-methyl pentasaccharide –Org-31540/SR-90107A or fondaparinux– was synthesized (2) in much better yield than the original synthetic pentasaccharide. The biological properties of both pentasaccharides (hydroxyl or methyl group on the H unit) were identical. Fondaparinux, therefore, is a novel sulfated pentasaccharide that is analogous to the high-affinity antithrombin binding sequence in heparin (3).

Pharmacological Actions

The mechanism of action of fondaparinux is related to the anticoagulant effect of heparins. The activity of unfractionated heparin and low-molecular-weight heparins, the two most widely used antithrombotic drugs, is essentially due to their ability to interact with antithrombin, a serine protease inhibitor present in plasma in a latent form (5). The interaction between heparin and antithrombin mainly results in inhibition of the coagulation enzymes thrombin (activated factor II) and factor Xa (5). Although antithombin is a natural anticoagulant, the efficient inhibition of proteases (mainly factor Xa and thrombin) by antithrombin requires heparin as cofactor (9). Upon heparin binding, antithrombin undergoes a conformational change which is sufficient to allow factor Xa inhibition (allosteric mechanism), whereas thrombin inhibition further requires binding of both antithrombin and thrombin to the same heparin molecule (template mechanism) (10). For this reason, thrombin inhibition requires a longer heparin chain than factor Xa inhibition (11).

The chain sequence of natural heparin comprises between 14 and 20 saccharide units (12). The minimum number of saccharide units in the heparin chain that could inhibit thrombin is 15. A pentasaccharide sequence, which represents the antithrombin binding site of heparin, is a potent and selective anti-factor Xa compound (13), and is present in only one-third of the heparin molecules (5). This pentasaccharide sequence, termed the antithrombin binding sequence, is the shortest fragment able to catalyze antithrombin-mediated factor Xa inhibition.

Fondaparinux is an exact copy of this pentasaccharide, the heparin sequence required for antithrombin binding, and therefore contains both glucuronic and iduronic acid units, and N-sulfated glucosamine. Fondaparinux, by selectively binding to antithrombin, induces a conformational change that specifically increases by a factor of about 340 the natural neutralization of factor Xa by antithrombin, resulting in dose-dependent inhibition of factor Xa but no effect on thrombin (3, 14, 15). Each molecule of fondaparinux binds to one molecule of antithrombin, but fondaparinux is then released from the antithrombin-activated factor complex, allowing it to consecutively bind to several antithrombin molecules. The antithrombin conformational change is permanent once the covalent complex with factor Xa is formed, and the enzyme-inhibitor complex is then cleared from the circulation. Fondaparinux is a highly selective and potent inhibitor of factor Xa, dependent upon antithrombin binding, and thereby inhibits the coagulation cascade, and consequently thrombin generation, thrombus formation and the growth of thrombi. The concentration of fondaparinux that inhibits 50% of factor Xa activity is 40 ± 3 nmol/l in humans, 45 ± 11 nmol/l in rabbits and 36 ± 12 nmol/l in rats (16). The dissociation constant (K_d) of the binary antithrombin-fondaparinux complex has been reported to be between 36 ± 11 nmol/l (3) and 48 ± 11 nmol/l in humans, 78 ± 2 nmol/l in rabbits and 50 ± 3 nmol/l in rats (16).

Heparin cofactor II is another plasma serine protease inhibitor that resembles antithrombin in that it can be activated by glycosaminoglycan binding. Fondaparinux only promotes small increases in heparin cofactor II-mediated antithrombin activity at a relatively high concentration compared to that required for antithrombin-mediated factor Xa inhibition (17).

In non-anticoagulated human whole blood, fondaparinux causes a concentration-dependent anticoagulant effect (18). Fondaparinux has no effect on the prothrombin time or thrombin clotting time and it has a very weak effect on the activated partial thromboplastin time (aPTT), but only at very high concentrations (15, 19). Fondaparinux inhibits thrombin generation *in vitro* (15). Thrombin generation following extrinsic pathway activation is inhibited to a greater extent than thrombin generation following intrinsic pathway activation, probably due to fondaparinux's inability to inhibit activated factor VIII formation due to its lack of antithrombin activity (15). *In vitro* data demonstrate a concentration-dependent reduction in thrombin generation in platelet-depleted plasma (19), associated with an increase in the lag phase. This concentration-dependent reduction reaches a plateau and the pentasaccharide does not cause complete thrombin inhibition.

The inhibition of thrombin generation has also been assessed *ex vivo* in human platelet-depleted plasma obtained from healthy volunteers receiving s.c. fondaparinux at doses of 6, 12 or 18 mg. A linear, dose-dependent inhibition of *ex vivo* thrombin generation was observed (17), with a plateau at 70% inhibition, suggesting that the inhibition cannot exceed a maximum level determined by plasma antithrombin (17). Although the dose-response reached a plateau *in vitro*, data from animal models indicate that complete inhibition is not necessary for an efficient antithrombotic effect (19).

Fondaparinux has little or no inhibitory effect on clot-bound factor Xa incorporated into the prothrombinase complex (20, 21), although it renders the surface of the thrombus less thrombogenic (22).

It has been demonstrated that the pentasaccharide-antithrombin complex inhibits the coagulant activity of the tissue factor-activated factor VII complex (23). In contrast to unfractionated heparin, tissue factor pathway inhibitor (TFPI; the main inhibitor of the factor VII-tissue factor complex) release is not induced in humans by fondaparinux (17). In addition, TFPI activity is not increased by the drug (24).

Contradictory data (indicating inactivation or no effect) concerning the effect of fondaparinux on activated factor IX have been reported (3).

Fondaparinux does not possess any thrombolytic activity itself *in vitro*, but it has been demonstrated that the drug is able to enhance clot lysis induced by tissue plasminogen activator (tPA) in rabbit models (25). Even at very high concentrations (100 μg/ml), fondaparinux does not cause spontaneous platelet aggregation or influence platelet aggregation (26). Fondaparinux does not bind to PF4 and does not promote heparin-induced thrombocytopenia (14, 16, 27). In an *in vitro* study performed using plasma from 25 patients with documented heparin-induced thrombocytopenia, an absence of cross-reactivity with pentasaccharide was observed (28). Another study performed in plasma from 49 patients with documented heparin-induced thrombocytopenia demonstrated that, regardless of concentration, fondaparinux does not enhance antibody binding to PF4 (29). These results support the hypothesis that a certain degree of sulfation, which is not present in fondaparinux, is required for a positive platelet response in heparin-induced thrombocytopenia (15).

The antithrombotic effects of fondaparinux after i.v. and s.c. administration have been assessed in various animal models (30). In a rabbit venous stasis thrombosis model using human serum as the thrombogenic stimulus, fondaparinux inhibited clot formation in a dose-dependent manner (31). Fondaparinux retained dose-dependent antithrombotic activity using different thrombogenic stimuli in rabbit models (32).

Two animal models mimicking arterial occlusion with platelet-rich thrombus have been assayed. In a rat arteriovenous shunt model, fondaparinux and heparin inhibited thrombus growth by 30% at an i.v. dose of 80 anti-Xa U/kg for both drugs after 15-min circulation through the shunt (15, 22). In a modified arteriovenous shunt model in nonhuman primates (baboons), fondaparinux significantly reduced platelet deposits in the arterial thrombosis model and fibrin in the venous thrombosis model (15, 33).

Treatment with fondaparinux enhanced thrombolysis in a model of venous thrombosis in rabbits (16), and in a study in dogs with coronary thrombosis, fondaparinux was as effective as unfractionated heparin in enhancing alteplase-induced thrombolysis (34).

In humans, no significant prolongation of the primary bleeding time is observed with any fondaparinux dose and a significant prolongation of aPTT is found only with very high doses (3, 15, 35).

Fondaparinux inhibits thrombin generation *in vivo* in humans, as shown by a decrease in the levels of the thrombin-antithrombin complex and prothrombin fragment 1+2 (36).

Pharmacokinetics and Metabolism

Preliminary pharmacokinetic studies of pentasaccharide in a primate (*Macaca mulatta*) model were published in 1985 (31). In humans, the pharmacokinetic properties and general tolerance of fondaparinux were evaluated in 3 consecutive phase I studies (35). In the first study, 9 groups of 6 young (18-35 years) healthy male volunteers were randomized to receive an s.c. injection of increasing doses of fondaparinux ranging from 0.36-28.6 mg (n = 4), placebo (n = 1) or heparin (n = 1) in a double-blind fashion (35). Doses of 0.72 mg or lower did not generate measurable plasma anti-factor Xa activity. In the second study, 6 consecutive groups of 5 elderly (65-85 years) healthy volunteers of both sexes were randomized to receive an s.c. injection of placebo (n = 1) or increasing doses of fondaparinux (n = 4) ranging from 0.71-17.2 mg (35). The lower dose did not generate measurable plasma anti-Xa activity. The half-life of fondaparinux was longer in the elderly and the mean apparent plasma clearance and renal clearance were lower. In the third study, 5 groups of 5 elderly healthy volunteers of both sexes were randomized to receive s.c. placebo (n = 1), fondaparinux s.c. every 24 h (5.7 or 11.4 mg) or fondaparinux s.c. every 12 h (2.9, 5.7 or 8.6 mg) for 7 consecutive days (35). The accumulation factors (measured as area under the curve at day 7/area under the curve at day 1) were 1.5 for once-daily fondaparinux and 2.3 for twice-daily fondaparinux. The peak steady-state concentrations were reached between days 2 and 3. Half-life, apparent plasma clearance and renal clearance were similar on days 1 and 7.

Phase I trials in healthy human volunteers have shown 100% bioavailability for s.c. fondaparinux (3, 35), as well as a rapid onset of action (t_{max} = 1.7 h).

Fondaparinux has a remarkably constant half-life (13.1-13.9 h) irrespective of the dose administered (35). The half-life of fondaparinux in rats, rabbits and baboons ranges from 1-4 h (37). The total apparent plasma clearance is not significantly dose-related, ranging from

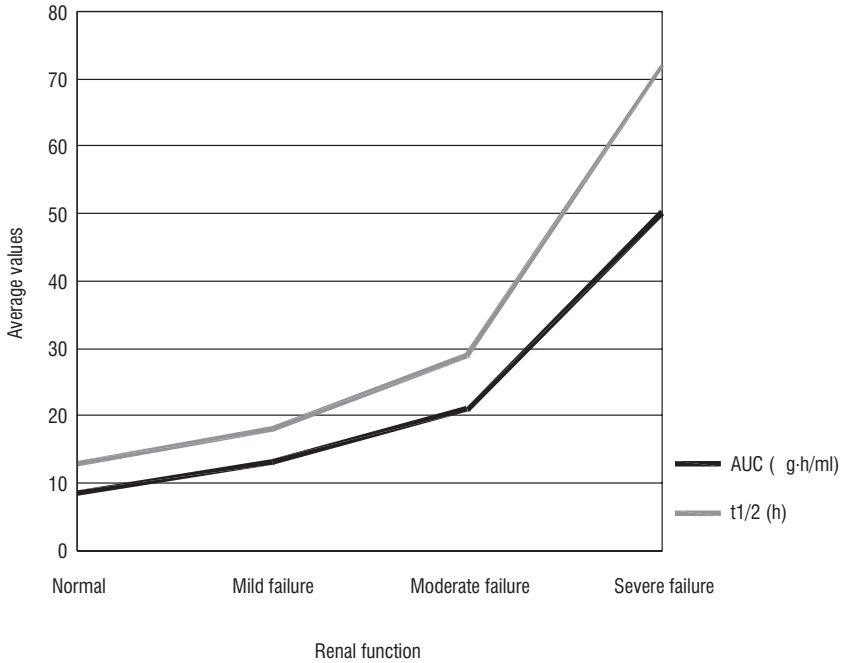

Fig. 1. Influence of renal function on the pharmacokinetics of fondaparinux.

7.3-9.2 mg/min. The volume of distribution ranges from 108-140 ml/kg (35).

Fondaparinux is not metabolized and is cleared almost exclusively by the kidneys as active substance (3, 15, 35). In rats, fondaparinux is cleared from the circulation by two mechanisms: unbound pentasaccharide is rapidly cleared by the kidneys, whereas fondaparinux bound to antithrombin is eliminated with the protein (38). The plasma antithrombin concentration is not modified by fondaparinux even after repeated doses (35). Renal clearance increases with dose, ranging from 5.0-9.0 ml/min (35). Renal clearance may be reduced in elderly patients, prolonging the elimination half-life. A significant correlation between creatinine clearance and fondaparinux renal clearance has been seen (35).

In humans with various renal function statuses, increasing degrees of renal impairment significantly prolong the elimination half-life ($t_{1/2}$) of fondaparinux, resulting in increasing values for the area under the concentration *vs.* time curve (AUC) (39) (Fig. 1).

The linear pharmacokinetics of fondaparinux show low variability and are highly reproducible and predictable (40), thus eliminating the need for laboratory monitoring (3).

Whereas low-molecular-weight heparin doses are expressed in anti-Xa units, doses of fondaparinux can be expressed in milligrams (mg). However, since no reliable chemical method to determine the concentration of fondaparinux is currently available, anti-Xa activity is employed to monitor the drug. Several clotting, amidolytic and chromogenic assays have been employed to estimate the anti-Xa potency of fondaparinux. Overall, it has been estimated that 1 mg of fondaparinux has a specific anti-Xa activity of approximately 850 IU (3, 16).

Clinical Studies

Several phase II and III studies have been published or are currently in progress on the efficacy and safety of fondaparinux for the prevention and treatment of venous thrombosis and arterial disease. The results of some of them are summarized in Table I.

Prevention of venous thromboembolism in orthopedic surgery

The phase II PENTATHLON trial was conducted in more than 900 patients undergoing total hip replacement and demonstrated significant, dose-dependent reductions in the frequency of venous thromboembolism (41). This trial was performed in Canada, the U.S. and Australia as a multicenter, double-blind evaluation of different doses of fondaparinux in comparison with the low-molecular-weight heparin enoxaparin. Patients were randomized to receive 1 of 5 doses of fondaparinux s.c. (0.75, 1.5, 3, 6 or 8 mg/24 h) administered 6 ± 2 h postoperatively, or enoxaparin s.c. (30 mg/12 h) beginning 12-24 h postoperatively. Ascending venography performed either at the end of treatment or before discharge and at clinical follow-up on day 40 was used to evaluate study endpoints. Efficacy was determined on an intent-to-treat basis in patients who underwent venography (73%). The

Table I: Clinical studies of fondaparinux sodium.

Indication	Design	Treatments	n	Conclusions	Ref.
Total hip replacement surgery, thrombo-embolism prophylaxis	Randomized, double-blind, dose-finding, multicenter	Fondaparinux, 0.75 mg sc od (initiated 6 h after surgery) x 5-10 d (n = 184) Fondaparinux, 1.5 mg sc od (initiated 6 h after surgery) x 5-10 d (n = 188) Fondaparinux, 3 mg sc od (initiated 6 h after surgery) x 5-10 d (n = 177) Fondaparinux, 6 mg sc od (initiated 6 h after surgery) x 5-10 d (n = 72) Fondaparinux, 8 mg sc od (initiated 6 h after surgery) x 5-10 d (n = 52) Enoxaparin, 30 mg sc bid (initiated 12-24 h before surgery) x 5-10 d (n = 260)	933	Fondaparinux 3 mg was more effective than enoxaparin but had slightly more major bleeding complications. Thus, a dose of 2.5 mg sc of fondaparinux might be the optimal dose in venous thromboembolism prophylaxis in total hip replacement	41
Hip fracture surgery, thrombo-embolism prophylaxis	Randomized, double-blind, multicenter	Fondaparinux, 2.5 mg sc od (initiated 6 h after surgery) x 5-9 d (n = 831) Enoxaparin, 40 mg sc od (initiated 12 h before surgery) x 5-9 d (n = 842)	1673	Fondaparinux was more effective than enoxaparin as a prophylactic agent in venous thromboembolism after hip fracture surgery	42
Major knee surgery, thrombo-embolism prophylaxis	Randomized, double-blind, multicenter	Fondaparinux, 2.5 mg sc od (initiated after surgery) x 5-9 d (n = 517) Enoxaparin, 30 mg sc bid (initiated after surgery) x 5-9 d (n = 517)	1034	Fondaparinux 2.5 mg once daily was more effective than enoxaparin 30 mg twice daily for the prevention of venous thromboembolism after major knee surgery	43
Total hip replacement surgery, thrombo-embolism prophylaxis	Randomized, double-blind, multicenter	Fondaparinux, 2.5 mg od x 7 d (starting postoperatively) Enoxaparin, 30 mg bid x 7 d (starting postoperatively)	2275	Fondaparinux was more effective than enoxaparin	44
Total hip replacement surgery, thrombo-embolism prophylaxis	Randomized double-blind, multìcenter	Fondaparinux, 2.5 mg od x 7 (starting postoperatively) Enoxaparin, 40 mg sc od x 7 d (starting preoperatively)	2309	Fondaparinux was safe, well tolerated and more effective than enoxaparin in the prophylaxis of venous thrombo-embolism in orthopedic patients undergoing primary total hip replacement or revision surgery	45
Myocardial infarction	Randomized, dose-finding, open, multicenter	Fondaparinux, 4 mg/d iv → Alteplase + Fondaparinux, 4 mg/d sc (6 mg if > 90 kg) + Aspirin, 150-325 mg/d po x 5-7 d (n = 81) Fondaparinux, 8 mg/d iv → Alteplase + Fondaparinux, 8 mg/d sc (6 mg if < 60 kg, 10 mg if > 90 kg) + Aspirin, 150-325 mg/d po x 5-7 d (n = 77) Fondaparinux, 12 mg/d iv → Alteplase + Fondaparinux, 12 mg/d sc (10 mg if < 60 kg) + Aspirin, 150-325 mg/d po x 5-7 d (n = 83) Heparin, 5000 IU iv bolus (4000 if ≤ 67 kg) → Alteplase + Heparin, 1000 IU/h iv infusion (800 IU/h if ≤ 67 kg) x 48-72 h + Aspirin, 150-325 mg/d po (n = 85)	326	Fondaparinux plus alteplase was as safe and effective as unfractionated heparin in restoring coronary artery patency in ST-segment elevation acute myocardial infarction	49

safety analysis included the entire cohort (933 patients). In the enoxaparin group, patients had a 9.4% incidence of deep venous thrombosis compared to values in the fondaparinux groups of 11.8, 6.7, 1.7, 4.4 and 0%, respectively. Although patients receiving 8 mg of fondaparinux had no thrombosis, in this group there was a disproportionate number of premature discontinuations for bleeding (17.3% major bleeding), and the same occurred with the 6-mg dose (16.3%). Although the study was not designed to compare enoxaparin and fondaparinux, the risk of venous thrombosis was reduced by 82% in the 3-mg fondaparinux group and a significantly lower risk of proximal venous thrombosis was seen compared to the enoxaparin group. The low major and minor bleeding rates occurring in the enoxaparin group (3.5 and 3.1%, respectively) were comparable to the rates seen in the 3-mg fondaparinux group (4.5 and 3.4%, respectively). Fondaparinux doses greater than 3 mg were associated with a significantly increased bleeding risk.

To determine the fondaparinux dose for comparative phase III trials with enoxaparin, a Logit model for efficacy and safety was applied and the optimal dose for efficacy was determined to be between 2 and 3 mg (41). Thus, a fondaparinux dose of 2.5 mg s.c. every 24 h was selected for phase III trials.

Four phase III trials designed to evaluate the efficacy and safety of fondaparinux compared with the low-molecular-weight heparin enoxaparin for the prevention of venous thromboembolism following orthopedic surgery have been conducted. These studies included 7000 major orthopedic patients in Europe, Latin America, Canada, Australia and the U.S. These phase III studies were known as PENTHIFRA (42), which included 1711 hip fracture surgery patients in Europe, South Africa, Argentina and Australia; PENTAMAKS (43), which included 1049 major knee surgery patients in North America; PENTATHLON 2000 (44), which included 2275 elective total hip replacement surgery patients in North America; and EPHESUS (45), which included 2309 elective total hip replacement surgery patients in Europe, Australia and Asia. These were prospective, multicenter, double-blind, randomized studies comparing s.c. fondaparinux (2.5 mg/24 h), starting 6 h after surgery, with s.c. enoxaparin at a dose of 30 mg every 12 h starting postoperatively in the PENTATHLON 2000 and PENTAMAKS trials, and a dose of 40 mg every 24 h starting preoperatively in the EPHESUS and PENTHIFRA trials. In the 4 studies, the primary efficacy endpoint was the occurrence of venous thromboembolism up to day 11, as determined by venography, and the main safety outcome was major bleeding. In total, 7344 patients were randomized. Efficacy was evaluated in 5385 (73.3%). The risk of venous thromboembolism was reduced by 50% in patients receiving fondaparinux compared with those receiving enoxaparin. There were no significant differences between the two treatments with regard to death and clinically important bleeding criteria (fatal bleeding, nonfatal bleeding in a critical organ or bleeding leading to reoperation).

The PENTHIFRA trial (42) demonstrated significantly superior efficacy for fondaparinux (8.3%) over enoxaparin (19.1%) following hip fracture surgery (56.4% relative risk reduction). The superior efficacy of fondaparinux was found when patients were grouped according to age, sex, body mass index, type of anesthesia, type of hip fracture, type of surgery or whether or not the patient had had previous venous thromboembolism. Major bleeding (2.2% in the fondaparinux group *vs.* 2.3% in the enoxaparin group), minor bleeding (4.1% *vs.* 3.1%) and reoperation due to bleeding (0.2% *vs.* 0.4%) were similar in both groups. Transfusion requirements and the incidence of other adverse events during treatment or follow-up did not differ significantly between groups.

The PENTAMAKS trial (43) demonstrated significantly superior efficacy for fondaparinux (12.5%) over enoxaparin (27.8%) following elective major knee surgery (55.2% relative risk reduction). There was no fatal bleeding or nonfatal bleeding in a critical organ in either treatment group. No statistically significant differences were seen in mortality (0.2% *vs.* 0.4%), but a higher incidence of major bleeding episodes was observed in the fondaparinux group (2.3%) compared to the enoxaparin group (0.2%). However, no differences were observed in bleeding leading to reoperation (0.4% *vs.* 0.2%).

In the PENTATHLON 2000 trial (44), fondaparinux showed a relative risk reduction of 26% compared to enoxaparin in the incidence of venous thromboembolism following elective hip replacement surgery. The safety profiles of the two agents were similar.

In the EPHESUS trial (45), significantly superior efficacy was seen for fondaparinux (4.0%) compared to enoxaparin (9.0%) following total hip replacement (56% relative risk reduction). No statistically significant differences were seen in safety.

Treatment of deep venous thrombosis

A randomized, parallel-group, dose-ranging phase II trial (Rembrandt study) was conducted to evaluate the efficacy and safety of 3 doses of fondaparinux (5, 7.5 and 10 mg/24 h s.c.) in comparison to the low-molecular-weight heparin dalteparin (100 IU/12 h s.c.) for the treatment of symptomatic proximal deep venous thrombosis (46). A total of 334 patients were treated with fondaparinux and 119 with dalteparin. The primary outcome measure was the change in thrombus mass, as determined by ultrasonography and perfusion lung scintigraphy. Similar efficacy (46.0, 48.1 and 41.7% reductions, respectively, in the fondaparinux groups *vs.* a 48.7% reduction in the dalteparin group) was observed with both drugs. The incidence of major bleeding was low and similar among the groups (3.9, 1.8 and 0.8%, respectively, *vs.* 2.5%), and fewer recurrences (1.9, 1.8 and 3.3%, respectively, *vs.* 5.0%) were seen in the fondaparinux-treated patients. The 2 patients with a recurrence during fondaparinux treatment received the lowest dose, whereas the only unusual major bleeding episode occurred in a patient

given the highest dose. Finally, after considering all the available information, including the perfusion lung scan and ultrasonography, the dose of 7.5 mg/24 h was selected for further phase III trials.

Based on these results, 2 large phase III trials have been initiated: the Matisse-DVT and the Matisse-PE trials. The Matisse-DVT trial is an ongoing double-blind comparison of fondaparinux and enoxaparin planned for 2200 patients with documented deep venous thrombosis. The other study, the Matisse-PE, is an open study comparing 2200 patients with acute pulmonary embolism treated with either fondaparinux or unfractionated heparin (47, 48).

Arterial disease

An open-label, pilot phase IIa study (36) assessed the effect of a single i.v. dose of fondaparinux (12 mg just before the procedure) in patients undergoing percutaneous transluminal coronary angioplasty without the use of heparin. The primary endpoint was the rate of abrupt vessel closure during and within 24 h after the procedure, and secondary endpoints were the need for revascularization, visual assessment of coronary angiography and bleeding complications. A total of 61 evaluable patients were included and abrupt vessel closure occurred in 3.3%. No major bleeding occurred. None of the patients needed emergency revascularization or suffered from Q or non-Q wave myocardial infarction. The angioplasty site was patent in all the patients at 24 h.

Based on the above study demonstrating the safety and efficacy of fondaparinux, its use in arterial disease is being investigated in two trials: PENTALYSE and PENTUA. PENTALYSE, conducted in patients with acute myocardial infarction, has been completed (49), but PENTUA, in unstable angina patients, is currently under way (47). In the PENTALYSE trial (49), the efficacy of fondaparinux during fibrinolytic therapy in 326 evaluable patients who had acute coronary syndromes with S-T segment elevation of less than 6 h duration was assessed. Study patients received aspirin and were randomly assigned to receive recombinant tissue-type plasminogen activator (alteplase) plus either unfractionated heparin or fondaparinux. Unfractionated heparin was administered i.v. (48-72 h) to 84 patients and fondaparinux was administered at 3 dose levels (4, 8 and 12 mg i.v. on day 1 and s.c. on days 2-5) to 232 patients. Coronary angiography at 90 min showed a slight but nonsignificant advantage for fondaparinux over unfractionated heparin in achieving TIMI grade 2 or TIMI grade 3 flow. Coronary angiography on days 5-7 showed the highest rates of TIMI grade 3 flow in the 8- and 12-mg fondaparinux groups. Prolonged administration of pentasaccharide was associated with a trend towards less reocclusion and fewer revascularizations. These results suggest that during the infusion of a fibrinolytic agent, thrombin activity probably does not need to be inhibited. This is consistent with the findings from the TAMI (Thrombolysis and Angioplasty in Myocardial Infarction) trial using unfractionated heparin (50). A nonsignificant dose-related increase in the rate of minor bleedings (mostly ecchymoses at the injection site or small groin hematomas at instrumented sites) was observed with fondaparinux use (49). Excluding transfusions related to bypass surgery, fewer blood transfusions were needed with fondaparinux: 3.3% *vs.* 7.1%. The incidences of death, myocardial infarction and intracranial bleeding were almost the same in all the groups. In conclusion, fondaparinux administered together with alteplase is safe and as effective as unfractionated heparin in restoring coronary artery patency (49).

The phase IIb PENTUA study, a dose-ranging clinical trial of fondaparinux in patients with acute coronary syndromes without S-T segment elevation, is currently under way in Europe. More than 1000 patients will be randomly assigned to receive 2.5, 4, 8 or 12 mg/24 h of fondaparinux or enoxaparin in a double-blind design. Endpoints are death, myocardial infarction and recurrent ischemia (47).

Toxicity

Fondaparinux appears to be a remarkably safe drug. It yields highly predictable plasma concentrations after s.c. administration (51) and, although pharmacokinetics are altered in patients with renal insufficiency, this is correlated with creatinine clearance and the dose can therefore be adjusted.

Although the predictable effect and antithrombin dependence of the drug may restrict side effects related to overdose, fondaparinux, as all anticoagulants, may cause bleeding. In several animal models, fondaparinux did not promote bleeding at doses more than 10-fold higher than the effective antithrombotic doses (15). Fondaparinux administered i.v. to rats in a tail transection model at 200-20,000 anti-Xa U/kg produced a slight increase in blood loss (maximum 2-fold more than placebo), whereas i.v. heparin at a dose of 300 anti-Xa U/kg caused a 5-fold increase in blood loss (52). In a rabbit ear bleeding model to determine the dose-response relationship for bleeding, fondaparinux did not significantly increase the amount of blood loss at doses 50-fold higher than the dose effective in the stasis thrombosis model (15).

In humans, fondaparinux has demonstrated a high degree of safety. In a phase I study (35), no spontaneous and no enhanced bleeding was seen after the administration of fondaparinux. When repeated injections of the drug were administered to elderly subjects, some minor hematomas at the injection site or mild transient hematuria was seen. At the highest doses studied, 26.6 or 11.4 mg for 7 days, rebleeding occurred in a limited number of patients following the accidental removal of the scar from the template bleeding time test when plasma levels were approximately 3.0 μg/ml (35).

In the phase II PENTATHLON trial in patients undergoing hip replacement, a dose-dependent increase in the

incidence of bleeding was observed and the 6 and 8 mg s.c./24 h fondaparinux groups were discontinued early due to respective rates of major bleeding of 16.3 and 17.3% (41). The risk of bleeding appears to be greater in patients with severe kidney disease, patients with very low body weight and patients of advanced age.

There is no definite antidote for fondaparinux. It is not neutralized by PF4 (14, 16), but the use of protamine sulfate (15), currently used to reverse the anticoagulant activity of heparin, has been suggested, although this drug is less efficient for reversing the action of the low-molecular-weight heparins. *In vitro* studies performed in human plasma showed no neutralization of fondaparinux activity at a 30-fold higher concentration of protamine compared to pentasaccharide (15). Although the effect of fondaparinux on coagulation cannot be reversed *in vitro* by protamine sulfate, in a rat model a significant reduction in blood loss was observed after protamine administration (53). Other possible antidotes for fondaparinux are heparinase I and polybrene. Heparinase I, a heparin lyase obtained from *Flavobacterium heparinum*, inactivates fondaparinux and reverses its anti-factor Xa activity by breaking it into inactive disaccharide and trisaccharide fragments, and has been suggested as a neutralizing agent for pentasaccharide overdose (54, 55). Polybrene neutralizes approximately 90% of the anti-factor Xa activity of fondaparinux at a 20/1 ratio (polybrene/fondaparinux, w/w) (15).

Fondaparinux is chemically synthesized and thus there is no risk of viral pathogen contamination, and batch-to-batch consistency is achievable because it is a homogeneous molecule (15).

Conclusions

The future of fondaparinux appears promising, although its clinical use and how it will compete with low-molecular-weight heparins remain to be determined. There are several potential advantages for specific factor Xa inhibitors like fondaparinux over thrombin inhibitors, particularly a higher safety margin in prophylaxis and less frequent dosing. It is most likely, however, that each drug will have a role in specific clinical indications and that one single drug will not be optimal for all thrombotic situations. As more is learned of the mechanisms of thrombosis, new drugs will be developed that target a patient's individual needs.

Fondaparinux was introduced in the U.S. in February as Arixtra® for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip fracture surgery, hip replacement surgery or knee replacement surgery. The product is supplied as an injectable solution for s.c. use containing 2.5 mg fondaparinux sodium in 0.5 ml of an isotonic solution of sodium chloride and water for injection. Marketing approval has also been recommended by the European authorities (56).

Source

Fondaparinux was developed under a collaboration between Sanofi-Synthelabo and Organon (Azko Nobel). The drug will be commercialized as part of a joint venture in the U.S., Canada and Mexico, and by Sanofi-Synthelabo in Europe and the rest of the word, excluding Japan.

References

1. van Boeckel, C.A.A., Petitou, M. *The unique antithrombin III binding domain of heparin: A lead to new synthetic antithrombotics.* Angew Chem In Ed Engl 1993, 32: 1671-90.

2. Petitou, M., Duchaussoy, P., Lederman, I., Choay, J., Sinäy, P., Jacquinet, J.C., Torri, G. *Synthesis of heparin fragments: A α-methyl α-pentaoside with high affinity for antithrombin III.* Carbohydr Res 1987, 167: 67-75.

3. Herbert, J.M., Petitou, M., Lormeau, J.C., Cariou, R., Necciari, J., Magnani, H.N., Zandberg, P., van Amsterdam, R.G.M., van Boeckel, C.A.A., Meuleman, D.G. *SR 90107A/Org 31540, a novel anti-factor Xa antithrombotic agent.* Cardiovasc Drug Rev 1997, 15: 1-26.

4. Bianchini, P., Liverani, L., Mascellani, G., Parma, B. *Heterogeneity of unfractionated heparins studied in connection with species, source, and production processes.* Semin Thromb Hemost 1997, 23: 3-10.

5. Hirsh, J., Warkentin, T.E., Shaughnessy, S.G., Anand, S.S., Halperin, J.L., Raschke, R., Granger, C., Ohman, E.M., Dalen, J.E. *Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety.* Chest 2001, 119: 64S-94S.

6. Choay, J., Lormeau, J.C., Petitou, M., Sinäy, P., Fareed, J. *Structural studies on a biologically active hexasaccharide obtained from heparin.* Ann NY Acad Sci 1981, 370: 644-9.

7. Sinäy, P., Jacquinet, J.E., Petitou, M., Duchaussoy, P., Lederman, I., Choay, J., Torri, G. *Total synthesis of a heparin pentasaccharide fragment having high affinity for antithrombin III.* Carbohydr Res 1984, 132: C5-C9.

8. Petitou, M., Duchaussoy, P., Lederman, I., Choay, J., Sinäy, P., Jacquinet, J.C., Torri, G. *Synthesis of heparin fragments. A chemical synthesis of the pentasaccharide O-(2-deoxy-2-sulfamido-6-O-sulfo-α-D-glucopyranosyl)-1→4)-O-(β-D-glucopyranosyluronic acid)-(1→4)-O-(2-deoxy-2-sulfamido-3, 6-di-O-sulfo-α-D-glucopyranosyl)-(1→4)-O-(2-O-sulfo-α-L-idopyranosyluronic acid)-(1→4)-2-deoxy-2-sulfamido-6-O-sulfo-D-glucopyranose decasodium salt, a heparin fragment having high affinity for antithrombin III.* Carbohydr Res 1986, 147: 221-36.

9. Jordan, R.E., Oosta, G.M., Gardner, W.T., Rosenberg, R.D. *The kinetics of hemostatic enzyme-antithrombin interactions in the presence of low molecular weight heparin.* J Biol Chem 1980, 255: 10081-90.

10. Olson, S.T., Björk, I. *Regulation of thrombin activity by antithrombin and heparin.* Semin Thromb Hemostasis 1994, 20: 373-409.

11. Casu, B. *Structure and biological activity of heparin.* Adv Carbohydr Chem Biochem 1985, 43: 51-134.

12. Laurent, T.C., Tengblad, A., Thunberg, L., Höök, M., Lindahl, U. *The molecular-weight-dependence of the anti-coagulant activity of heparin.* Biochem J 1978, 175: 691-701.

13. Choay, J., Petitou, M., Lormeau, J.C., Sinäy, P., Casu, B., Gatti, G. *Structure-activity relationship in heparin: A synthetic pentasaccharide with high affinity for antithrombin III and eliciting high anti-factor Xa activity.* Biochem Biophys Res Commun 1983, 116: 492-9.

14. Olson, S.T., Björk, I., Sheffer, R., Craig, P.A., Shore, J.D., Choay, J. *Role of the antithrombin-binding pentasaccharide in heparin acceleration of anti-thrombin-proteinase reactions: Resolution of the antithrombin conformational change contribution to heparin rate enhancement.* J Biol Chem 1992, 267: 12528-38.

15. Walenga, J.M., Jeske, W.P., Bara, L., Samama, M.M., Fareed, J. *Biochemical and pharmacologic rationale for the development of a synthetic heparin pentasaccharide.* Thromb Res 1997, 86: 1-36.

16. Herbert, M., Hérault, J.P., Bernat, A., van Amsterdam, R.G., Vogel, G.M., Lormeau, J.C., Petitou, M., Meuleman, D.G. *Biochemical and pharmacological properties of SANORG 32701. Comparison with the 'synthetic pentasaccharide' (SR 90107/ORG 31450) and standard heparin.* Circ Res 1996, 79: 590-600.

17. Lormeau, J.C., Hérault, J.P. *The effect of the synthetic pentasaccharide SR 90107/ORG 31540 on thrombin generation ex vivo is uniquely due to ATIII-mediated neutralization of factor Xa.* Thromb Haemost 1995, 74: 1474-7.

18. Bendayan, P., Boccalon, H., Dupouy, D., Boneu, B. *Dermatan sulfate is a more potent inhibitor of clot-bound thrombin than unfractionated and low molecular weight heparins.* Thromb Haemost 1994, 71: 576-80.

19. Walenga, J.M., Bara, L., Petitou, M., Samama, M., Fareed, J., Choay, J. *The inhibition of the generation of thrombin and the antithrombotic effect of a pentasaccharide with sole anti-factor Xa activity.* Thromb Res 1988, 51: 23-33.

20. Hemker, H., Choay, J., Beguin, S. *Free factor Xa is on the main pathway of thrombin generation in clotting plasma.* Biochem Biophys Acta 1989, 992: 409-11.

21. Visser, A., Meuleman, D. *Inhibition of the early stages of the thrombin generation reaction by various glycosaminoglycans.* Thromb Res 1990, 58: 469-74.

22. Vogel, G.M., van Amsterdam, R.G., Kop, W.J., Meuleman, D.G. *Pentasaccharide and Orgaran arrest, whereas heparin delays thrombus formation in a rat arteriovenous shunt.* Thromb Haemost 1993, 69: 29-34.

23. Lormeau, J.C., Hérault, J.P., Herbert, J.M.. *Antithrombin mediated inhibition of factor VIIa-tissue factor complex by the synthetic pentasaccharide representing the heparin binding site to AT.* Thromb Haemost 1996, 76: 5-8.

24. Kaiser, B., Hoppensteadt, D.A., Jeske, W., Wun, T.C., Fareed, J. *Inhibitory effects of TFPI on thrombin and factor Xa generation in vitro-modulatory action of glycosaminoglycans.* Thromb Res 1994, 75: 609-16.

25. Bernat, A., Hoffmann, P., Sainte-Marie, M., Herbert, J.M. *The synthetic pentasaccharide SR 90107A/Org 31540 enhances tissue-type plasminogen activator-induced thrombolysis in rabbits.* Fibrinolysis 1996, 10: 151-7.

26. Salzman, E.W., Rosenberg, R.D., Smith, M.H., Lindon, J.N., Favreau, L. *Effect of heparin and heparin fractions on platelet aggregation.* J Clin Invest 1980, 65: 64-73.

27. Ahmad, S., Jeske, W.P., Walenga, J.M., Hoppensteadt, D.A., Wood, J.J., Herbert, J.M., Messmore, H.L., Fareed, J. *Synthetic pentasaccharides do not cause platelet activation by antiheparin-platelet factor 4 antibodies.* Clin Appl Thromb Hemost 1999, 5: 259-66.

28. Elalamy, I., LeCrubier, C., Potevin, F., Abdelouahed, M., Bara, L., Marie, J.P., Samama, M. *Absence of in vitro cross-reaction of pentasaccharide with the plasma heparin-dependent factor of twenty-five patients with heparin-associated thrombocytopenia.* Thromb Haemost 1995, 74: 1384-5.

29. Amiral, J., Lormeau, J.C., Marfaing-Koka, A. et al. *Absence of cross-reactivity of SR90107A/ORG31540 pentasaccharide with antibodies to heparin-PF4 complexes developed in heparin-induced thrombocytopenia.* Blood Coagul Fibrin 1997, 8: 114-7.

30. Amar, J., Caranobe, C., Sié, P., Boneu, B. *Antithrombotic potencies of heparins in relation to their antifactor Xa and antithrombin activities: An experimental study in two models of thrombosis in the rabbit.* Br J Haematol 1990, 76: 94-100.

31. Walenga, J.M., Fareed, J. *Preliminary biochemical and pharmacological studies on a chemically synthesized pentasaccharide.* Semin Thromb Hemost 1985, 11: 89-99.

32. Walenga, J.M., Petitou, M., Lormeau, J.C., Samama, M., Fareed, M., Choay, J. *Antithrombotic activity of a synthetic heparin pentasaccharide in a rabbit stasis thrombosis model using different thrombogenic challenges.* Thromb Res 1987, 46: 187-98.

33. Cadroy, Y., Hanson, S.R., Harker, L.A. *Antithrombotic effects of synthetic pentasaccharide with high affinity for plasma antithrombin III in non human primates.* Thromb Haemost 1993, 70: 631-5.

34. Pislaru, S., Pislaru, C., Zhu, X., Arnout, J., Stassen, T., Vanhove, P., Herbert, J.M., Meuleman, D.G., van de Werf, F. *Comparison of a synthetic antithrombin III-binding pentasaccharide and standard heparin as an adjunct to coronary thrombolysis.* Thromb Haemost 1998, 79: 1130-5.

35. Boneu, B., Necciari, J., Cariou, R., Sié, P., Gabaig, A.M., Kieffer, G., Dickinson, J., Lamond, G., Moelker, H., Mant, T., Magnani, H. *Pharmacokinetics and tolerance of the natural pentasaccharide (SR90107/Org31540) with high affinity to antithrombin III in man.* Thromb Haemost 1995, 74: 1468-73.

36. Vuillemenot, A., Schiele, F., Meneveau, N., Claudel, S., Donat, F., Fontecave, S., Cariou, R., Samama, M.M., Bassand, J.P. *Efficacy of a synthetic pentasaccharide, a pure factor Xa inhibitor, as an antithrombotic agent: A pilot study in the setting of coronary angioplasty.* Thromb Haemost 1999, 81: 214-20.

37. Crépon, B., Donat, F., Barzu, T., Hérault, J.P. *Pharmacokinetic (PK) parameters of AT binding pentasaccharides in three animal species: Predictive value for humans.* Thromb Haemost 1993, 69: Abst 654.

38. van Amsterdam. R.G.M., Vogel, G.M.T., Visser, A., Kop, W.J., Buiting, M.T., Meuleman, D.G. *Synthetic analogues of the antithrombin III-binding pentasaccharide sequence of heparin. Prediction of in vivo residence times.* Arterioscler Thromb Vasc Biol 1995, 15: 495-503.

39. Faaij, R.A., Burggraaf, J., Schoemaker, H.C., Stiekema, J., Siegert, C.K, Cohen, A.F. *The influence of renal function on the pharmacokinetics (PK) and pharmacodynamics of the novel*

antithrombotic agent Org31540/SR90107A. Br J Clin Pharmacol 1998, 45: 211P.

40. Bauer, K.A. *Fondaparinux sodium: A selective inhibitor of factor Xa.* Am J Health-Syst Pharm 2001, 58 (Suppl. 2): S14-S17.

41. Turpie, A.G.G., Gallus, A.S., Hoek, J.A. *A synthetic pentasaccharide for the prevention of deep-vein thrombosis after total hip replacement.* N Engl J Med 2001, 344: 619-25.

42. Eriksson, B.I., Bauer, K.A., Lassen, M.R., Turpie, A.G.G. *Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after after hip-fracture surgery.* N Engl J Med 2001, 345: 1298-304.

43. Bauer, K.A., Eriksson, B.I., Lassen, M.R., Turpie, A.G.G. *Fondaparinux compared with enoxaparin for the prevention of venous thromboembolism after elective major knee surgery.* N Engl J Med 2001, 345: 1305-10.

44. Turpie, A.G.G. *Efficacy of the first synthetic factor Xa inhibitor, pentasaccharide Org31540/SR90107A, with low molecular weight heparin (LMWH) in the prevention of venous thromboembolism (VTE) following elective hip replacement surgery: The PENTATHLON 2000 Study.* Thromb Haemost 2001, 86 (Suppl.): Abst OC48.

45. Lassen, M.R. *Efficacy of the first syntetic factor Xa inhibitor, pentasaccharide Org31540/SR90107A, with low molecular weight heparin (LMWH) in the prevention of venous thromboembolism (VTE) following elective hip replacement surgery: The EPHESUS Study.* Thromb Haemost 2001, 86 (Suppl.): Abst OC45.

46. The Rembrandt Investigators. *Treatment of proximal deep vein thrombosis with a novel synthetic compound (SR90107A/ORG31540) with pure anti-factor Xa activity: A phase II evaluation.* Circulation 2000, 102: 2726-31.

47. Turpie, A.G.G. *Pentasaccharide Org31540/SR90107A clinical trials update: Lessons for practice.* Am Heart J 2001, 142: S9-S15.

48. Turpie, A.G.G. *Setting a standard for venous thromboembolism prophylaxis.* Am J Health-Syst Pharm 2001, 58 (Suppl. 2): S18-S23.

49. Coussement, P.K., Bassand, J.P., Convens, C., Vrolix, M., Boland, J., Grollier, G., Michels, R., Vahanian, A., Vanderheyden, M., Rupprecht, H.J., van de Werf, F. *A synthetic factor-Xa inhibitor (ORG31540/SR9017A) as an adjunct to fibrinolysis in acute myocardial infarction: The PENTALYSE study.* Eur Heart J 2001, 22: 1716-24.

50. Topol, E.J., George, B.S., Kereiakes, D.J., Stump, D.C., Candela, R.J., Abbottsmith, C.W., Aronson, L., Pickel, A., Boswick, J.M., Lee, K.L.et al. *A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction.* Circulation 1989, 79: 281-6.

51. Porcari, A.R., Chi, L., Leadley, R. *Recent advances in clinical trials of the direct and indirect selective factor Xa inhibitors.* Exp Opin Invest Drugs 2000, 9: 1595-600.

52. Hobbelen, P.M.J., van Dinther, T.G., Vogel, G.M.T., van Boeckel, C.A.A., Moelker, H.T.T., Meuleman, D.G. *Pharmacological profile of the chemically synthesized antithrombin III binding fragment of heparin (pentasaccharide) in rats.* Thromb Haemost 1990, 63: 265-70.

53. Bernat, A., Herbert, J.M. *Protamine sulfate inhibits pentasaccharide (SR 80027)-induced bleeding without affecting its antithrombotic and anti-factor Xa activity in the rat.* Haemostasis 1996, 26: 195-202.

54. Yu, G., LeBrun, L., Gunay, N.S., Hoppensteadt, D., Walenga, J.M., Fareed, J., Linhardt, R.J. *Heparinase I acts on a synthetic heparin pentasaccharide corresponding to the antithrombin III binding site.* Thromb Res 2000, 100: 549-56.

55. Daud, A.N., Ahsan, A., Iqbal, O., Walenga, J.M., Silver, P.J., Ahmad, S., Fareed, J. *Synthetic heparin pentasaccharide depolymerization by heparinase I: molecular and biological implications.* Clin Appl Thromb Hemost 2001, 7: 58-64.

56. *Arixtra introduced in the U.S. for preventing thromboembolic events following surgery.* DailyDrugNews.com (Daily Essentials) Feb 11, 2002.