Drugs of the Future 1999, 24(3): 261-268

CCC: 0377-8282/99

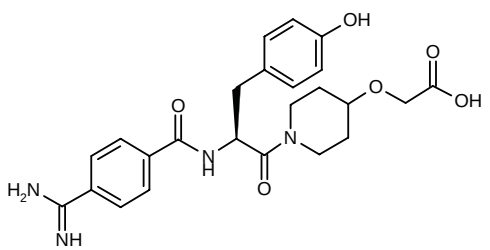
Lamifiban

Rec. INN; USAN

Platelet Antiaggregatory
Fibrinogen gpIIb/IIIa Receptor Antagonist

Ro-44-9883

2-[1-[*N*-(4-Amidinobenzoyl)-L-tyrosyl]piperidin-4-yloxy]acetic acid



$C_{24}H_{28}N_4O_6$ Mol wt: 468.514

CAS: 144412-49-7

EN: 191158

Synthesis

The acylation of 4-hydroxypiperidine (I) with benzyl chloroformate (II) by means of triethylamine in dichloromethane gives 4-hydroxypiperidine-1-carboxylic acid benzyl ester (III), which is condensed with *tert*-butyl bromoacetate (IV) by means of tetrabutylammonium hydrogensulfate and NaOH in toluene/water, affording 2-[1-(benzyloxycarbonyl)piperidin-4-yloxy]acetic acid *tert*-butyl ester (V). The deprotection of (V) by hydrogenation with H_2 over Pd/C in ethanol gives the piperidine (VI), which is condensed with *N*-(benzyloxycarbonyl)-4-*O*-*tert*-butyl-L-tyrosine (VII) by means of 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine (NMM) in dichloromethane, yielding the expected condensation product (VIII). The deprotection of the amino group of (VIII) by hydrogenation as before affords (IX), which is *N*-acylated with 4-amidinobenzoyl chloride (X), prepared by reaction of 4-amidinobenzoic acid (XI) with $SOCl_2$, giving the bis-*tert*-butylated product (XII). Finally, this compound is deprotected by means of trifluoroacetic acid in dichloromethane (1, 2). Scheme 1.

Description

Crystals, m.p. over 200 °C (decomp.), $[\alpha]_D^{20}$ +29.8° (c 0.86, 1N HCl) (1); trifluoroacetate salt, crystals, m.p. 125-30 °C (2).

Introduction

Several serious cardiovascular disorders such as myocardial infarction and unstable angina have been shown to be related to the activation of platelets and the resulting aggregation that leads to endovascular thrombus formation. The thrombosis is generally formed by activated platelets that adhere and aggregate at the site of endothelial cells. Currently available antiplatelet agents include aspirin, which inhibits prostaglandin production, and ticlopidine, which predominantly interferes with the ability of ADP to stimulate platelets.

Many new antithrombotic approaches are currently under clinical investigation, and are focused particularly on the direct inhibition of thrombin or on the platelet membrane receptor glycoprotein gpIIb/IIIa. The binding of fibrinogen to the gpIIb/IIIa receptor is considered the final common pathway for platelet aggregation. Inhibition of platelet aggregation induced by any agonist, including thrombin, is achieved by gpIIb/IIIa antagonism. The clinical potential of this new therapeutic approach culminated in the introduction of the chimeric MAb Fab fragment c7E3, abciximab (ReoPro®; Centocor/Lilly) in 1995 for the prevention of acute ischemic complications in patients undergoing PTCA (3). The pharmacological actions of various gpIIb/IIIa antagonists were recently summarized in this journal (4).

During the past year, the first two synthetic fibrinogen antagonists reached the market. Merck & Co.'s tirofiban hydrochloride (Aggrastat®) and Cor Therapeutics' eptifi-

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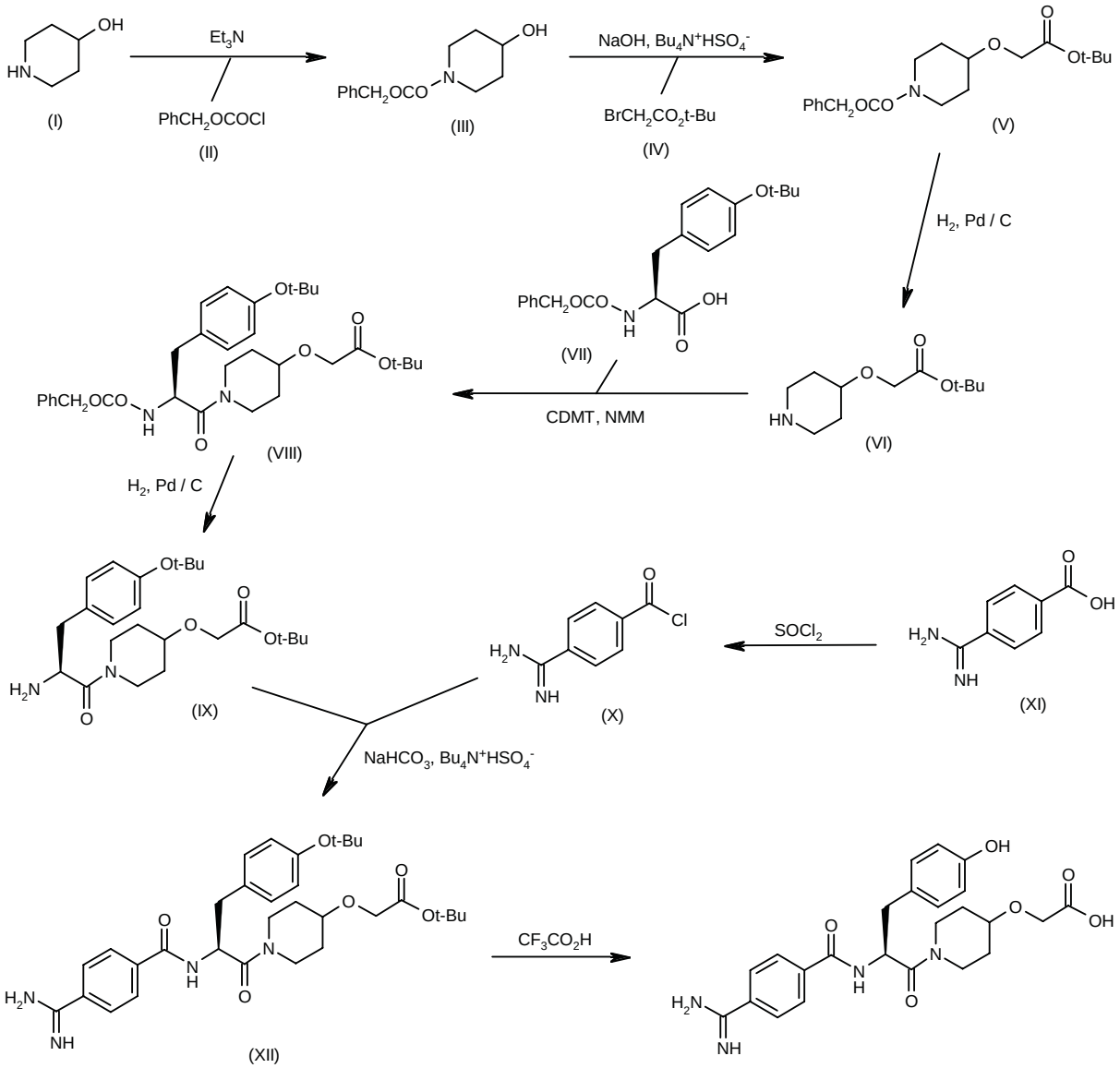
Scheme 1: Synthesis of Lamifiban



batide (Integrilin™) were launched in the U.S. in late May and early June, respectively. Both are indicated for the treatment of acute coronary syndrome. Several fibrinogen antagonists have progressed in clinical trials or have advanced to clinical testing within the last year and a half. One of these, Sanofi's SR-121787, has been claimed to be the most potent gpIIb/IIIa antagonist identified to date. This compound recently entered phase II clinical trials. Other compounds in clinical testing are given in Table I.

On the other hand, at least three compounds were recently discontinued. Based on the findings of the EXCITE and OPUS-TIMI 16 trials, Searle (Monsanto) recently announced its decision to discontinue all further development of xemilofiban and orbofiban acetate. No significant clinical benefit could be demonstrated in these two major studies with the Searle compounds, both of which had reached phase III testing. Late last year, Rhône-Poulenc Rorer made a similar decision to discontinue testing of RPR-109891 (Klerval™), which had also reached phase III. Although initial clinical results obtained with RPR-109891 were promising, the high doses necessary to obtain therapeutic levels of platelet inhibition made the product economically unfeasible (5).

Table I: Fibrinogen antagonists launched or under active investigation (from Prous Science Ensemble database).

Launched

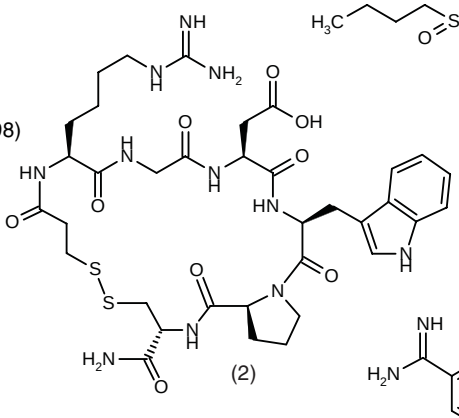
1. Abciximab
   ReoPro
   Centocor; Lilly (1995)
2. Eptifibatide
   Integrilin
   Cor Therapeutics; Schering-Plough (1998)
3. Tirofiban HCl
   Aggrastat
   Merck & Co. (1998)

Clinical Trials

4. CT-50352*
   Cor Therapeutics
5. FK-633
   Fujisawa
6. Fradafiban
   Boehringer Ingelheim
7. GR-233548
   Glaxo Wellcome
8. Lamifiban
   Roche
9. Lefradafiban
   Boehringer Ingelheim
10. Lotrafiban
    SmithKline Beecham
11. RWJ-533078
    R.W. Johnson
12. S-1197
    Hoechst Marion Roussel
13. SDZ-GPI-562
    Novartis
14. Sibrafiban
    Roche; Genetech
15. SR-121787
    Sanofi
16. T-250
    Toyama
17. TA-993
    Tanabe Seiyaku
18. TAK-029
    Takeda
19. YM-028/EMD-122-347
    Yamanouchi; Merck KGaA
20. YM-337
    Yamanouchi

MAb against gpIIb/IIIa receptor

(1)



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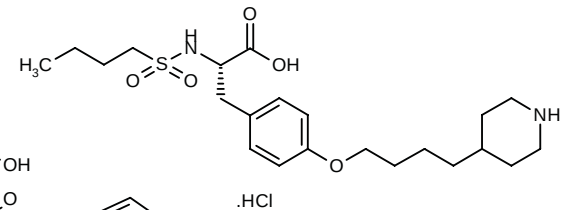
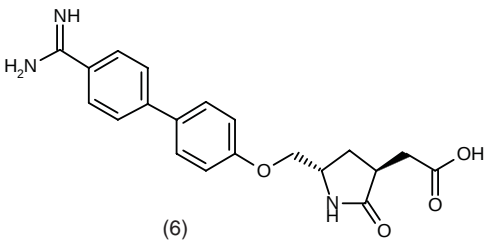


.HCl

(3)



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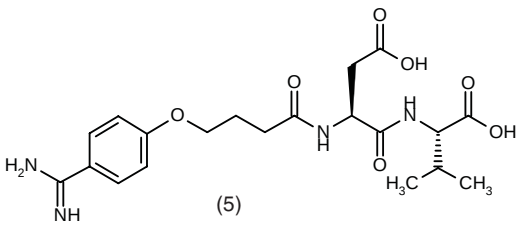

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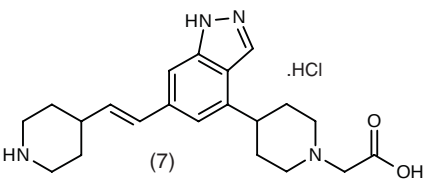

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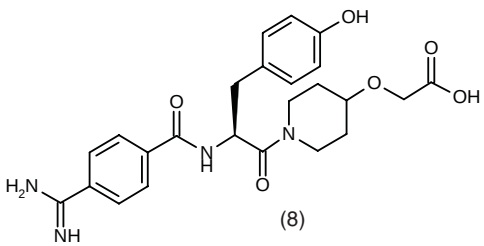

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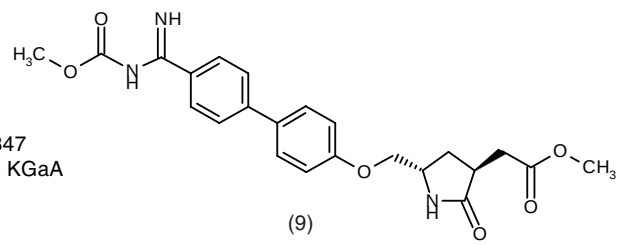

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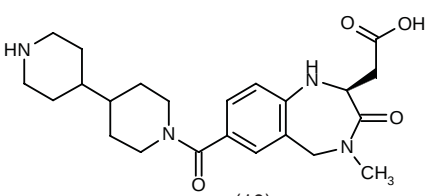

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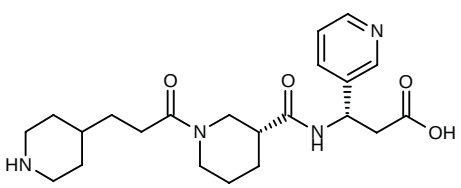

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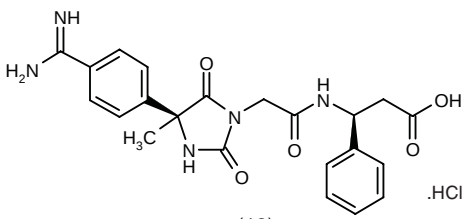

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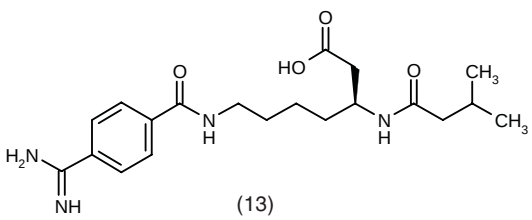

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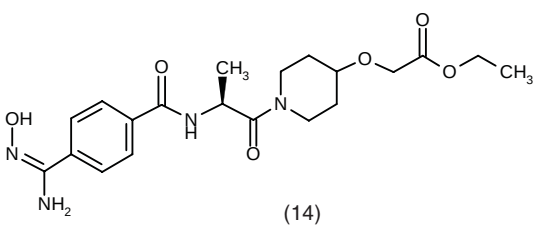

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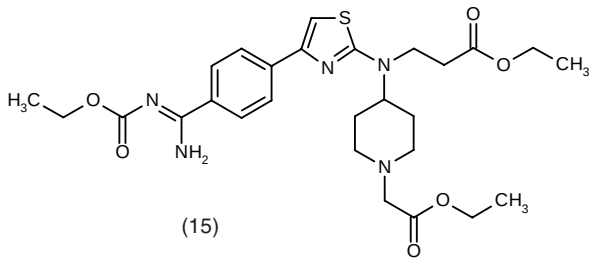
Table I: Continued.



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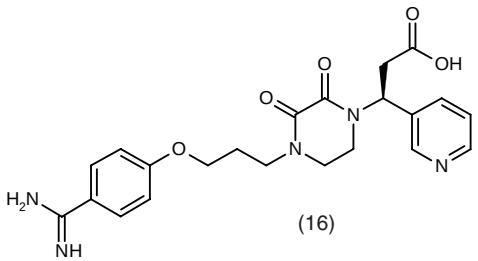

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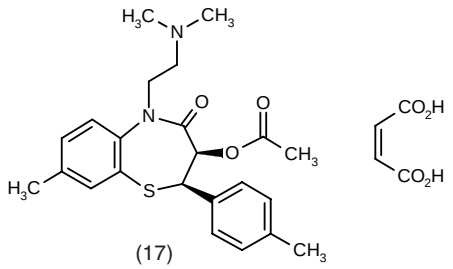

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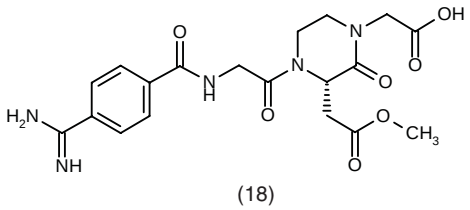

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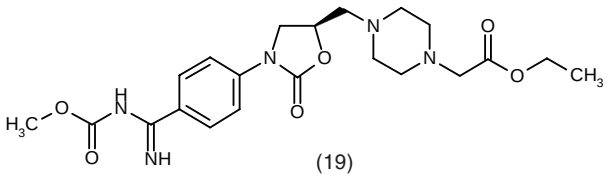

(19)

Humanized anti-gpIIb/IIIa MAb

(20)

*Structure not yet detected

Pharmacological Actions

Lamifiban (Ro-44-9883), a nonpeptide glycoprotein (gp) IIb/IIIa receptor antagonist, potently inhibited ADP-, collagen- and thrombin-induced platelet aggregation in human platelet rich plasma, with IC_{50} values of 0.03, 0.02 and 0.03 μM, respectively (1). It also inhibited platelet aggregation induced by the strong thrombin receptor agonist peptide (TRAP), with an IC_{50} value of 86 nM (6). Lamifiban, as well as other gpIIb/IIIa antagonists such as tirofiban and MK-852, showed higher affinity for activated than for resting platelets (K_d = 0.96 and 6.3 nM, respectively). On the contrary, the naturally occurring disintegrin echistatin and the synthetic compound L-736622 showed similar binding affinity for both forms (7). In solid-phase assays using purified gpIIb/IIa or $\alpha_v\beta_3$ receptors, lamifiban showed marked selectivity for the former (>100 million-fold) (1). In a solid-phase assay, the binding of the peptide RGDV and the peptidomimetic Ro-43-5054 to purified gpIIb/IIIa induced a high-affinity binding site for fibrinogen and the exposure of at least five neoepitopes (known as ligand-induced binding sites or LIBS), whereas lamifiban did not (8, 9). The gpIIb/IIIa antagonists such as lamifiban, which do not induce conformational changes upon binding, are much better inhibitors of platelet adhesion to fibrinogen than compounds that strongly induce LIBS. Thus, the IC_{50}s for platelet adhesion to fibrinogen were 652 ± 227 nM for Ro-43-5054 and 29 ± 9 for lamifiban, whereas their inhibition of gpIIb/IIIa binding to immobilized fibrinogen was similar (IC_{50}s = 2.3 and 1.6 nM for Ro-43-5054 and lamifiban, respectively) (10). Similar results were obtained *in vivo*, as lamifiban produced greater suppression of platelet activity than Ro-43-5054 in a canine model of coronary thrombolysis induced by tissue-plasminogen activator (t-PA). Nevertheless, this did not result in any discernible functional benefit *in vivo* (11, 12).

In a human *ex vivo* thrombosis model in which collagen-coated coverslips were exposed to flowing nonanticoagulated blood (shear rate, 65/s) for 5.5 min, lamifiban infusion (50 mcl/min, 500 nM) completely abrogated platelet thrombus formation but left the collagen-adherent platelet layer intact (13).

In *in vivo* animal studies, pretreatment with lamifiban (5, 10 and 20 μg/kg/min, i.v.) 30 min before photochemically induced thrombosis in the guinea pig femoral artery dose-dependently prolonged the time required for artery occlusion. In the same model, lamifiban given concomitantly with t-PA protected the early reocclusion after successful reperfusion (14). In guinea pigs undergoing extracorporeal circulation (arterio-arterial shunt from the aortic arch to the descending aorta), lamifiban, given as intravenous bolus, dose-dependently prevented the drop in platelet count at 30 and 60 min (control: 35 ± 4% and 25 ± 3% of initial value; 1 mg/kg lamifiban, 69 ± 8% and 54 ± 9%; 7 mg/kg lamifiban, 97 ± 8 and 80 ± 7%). All animals received 800 U/kg i.v. of heparin 30 min before starting the extracorporeal circulation (15). In a model of

cardiopulmonary bypass (ascending aorta to right atrial appendage) in heparinized dogs, the administration of 870 μg/kg i.v. of lamifiban completely prevented the drop in platelet count (53 ± 15% of initial levels in controls) at the start of cardiopulmonary bypass. Lamifiban at a lower dose, 145 μg/kg i.v., provided partial prevention. Although the high dose of lamifiban produced a significant increase in bleeding time, blood loss was similar in control and lamifiban-treated groups (16). Lamifiban (360 μg/kg i.v. administered 5 min before reperfusion plus 6 μg/kg/min until sacrifice) reduced infarct size (22.0 ± 5.3% *vs.* 41.4 ± 6.3% in controls, $p < 0.05$) in a model of ischemia (left anterior descending coronary artery, 90 min) followed by 6 h reperfusion under residual critical stenosis in anesthetized dogs. This beneficial effect was associated with a 48% reduction of 111In-platelet deposition in the infarct zone (17).

Pharmacokinetics and Metabolism

Preliminary studies showed that after intravenous administration in dogs lamifiban was eliminated according to a two-compartment model ($t_{1/2\alpha}$ = 8 min, $t_{1/2\beta}$ = 110 min) (1). Lamifiban demonstrated low oral absorption in animal studies, probably because of the two charged groups of the molecule (18). The pharmacokinetic profile of lamifiban in man was predicted from animal data by using allometric scaling and concentration-time transformations. Pharmacokinetic data for rats, dogs, cynomolgus monkeys and humans was: half-life = 0.45, 2.1, 1.4 and 2.1 h; total clearance = 2.6, 105, 8.3 and 134 ml/min and volume of distribution at steady-state = 0.066, 11.25, 0.928 and 20.3 l. Most of the clearance occurred by excretion of the unchanged compound in bile and, most importantly, in urine. Lamifiban was weakly bound to plasma proteins (6, 11 and 8% in humans, dogs and rats, respectively) (19, 20).

Clinical Studies

In a randomized, placebo-controlled study, the pharmacodynamics and pharmacokinetics of lamifiban were assessed in 34 healthy volunteers. Lamifiban was administered in ascending doses by a continuous 30-min infusion (0.03-1.0 μg/kg/min). Lamifiban inhibited ADP-induced platelet aggregation in a concentration-dependent manner, showing 50% inhibition at a free plasma concentration of 6.1 nM. The bleeding time (measured by a modification of the Ivy method) concentration effect curve was to the right of that for platelet aggregation inhibition. The mean pharmacokinetic parameters found in this study were volume of distribution = 22 l; half-life of free drug = 40 min; half-life of bound drug = 9.5 h and clearance = 25 l/h (21). Plasma levels of lamifiban resulting in 80% inhibition of ADP-induced platelet aggregation inhibited platelet aggregation induced by TRAP (0.1 mM) by only 15% and had no effect on the prolongation of bleeding time (6).

As lamifiban is eliminated almost exclusively by the renal route (90%, unchanged drug), a phase I study was performed in 16 patients with variable degrees of renal impairment. Patients with severe renal impairment (creatinine clearance 10-29 ml/min) showed decreased drug clearance and increased sensitization to the antiplatelet effects of the drug, thus allowing an 18-fold dosage reduction without compromising the pharmacodynamics (22).

A flow cytometric method based on the displacement by lamifiban of a fluorescein isothiocyanate-labeled ligand was developed to monitor lamifiban plasma concentrations in clinical trials (23, 24). In a preliminary efficacy study, 17 patients with unstable angina were randomized to lamifiban (1, 2, 4 or 5 μg/min) or placebo for a maximum of 120 h. Only high doses (4-5 μg/min) of lamifiban producing > 95% inhibition of ADP-induced platelet aggregation reduced the amount of ischemia, measured as ST segment displacement ≥ 50 μV lasting for ≥ 3 min (25).

The Canadian Lamifiban Study, a double-blind, randomized, dose finding study, compared the efficacy of infusions of lamifiban (1, 2, 4 or 5 μg/min for 72-120 h) with placebo in preventing ischemic events in 365 patients with unstable angina. Concomitant aspirin was administered to all patients (325 mg/day p.o.). The primary endpoints of the study were death, myocardial infarction and the need for urgent revascularization during the infusion period and after 1 month. Lamifiban treatment reduced combined endpoints by 60% (3.3% *vs.* 8.1%, $p < 0.04$). There was a dose-dependent inhibition of platelet aggregation and prolongation of bleeding time. Major bleeding occurred in 2.9% of patients receiving lamifiban and 0.8% of patients on placebo (26). This study served as the dose-ranging trial for the larger-scale PARAGON A trial.

In the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON A) trial, 2282 patients with unstable angina and non-Q-wave myocardial infarction were randomly assigned to receive aspirin plus either heparin (control group) or lamifiban (1 or 5 μg/min). Patients receiving lamifiban were then randomly assigned to subgroups receiving either heparin or no heparin (2x2 factorial design). No significant differences were found among the five arms of the study with regard to death rate or rate of myocardial infarction at 30 days. However, at 6 months, patients receiving the 1-μg dose of lamifiban plus heparin had a significant reduction in the rate of death or myocardial infarction compared with the control group (12.6% *vs.* 17.9%, $p < 0.02$) (27). No efficacy and an additional risk of bleeding complications was found in the 5-μg lamifiban plus heparin group (28). Favorable tendencies seen with low-dose lamifiban treatment at 6 months were further confirmed at 1 year follow-up, showing 16% reduction in mortality as compared to controls (29). Analyzing data for diabetic patients (n = 412), the beneficial effects of lamifiban treatment (all groups included for analysis) were even more evident, producing reductions

in the composite adverse event rate of 29% and 36% at 30 days and 6 months, respectively (16.7% lamifiban, 26.2% control, $p < 0.01$) (30). In a subset of patients who underwent percutaneous transluminal coronary angioplasty (n = 306), the incidence of death and myocardial infarction at 30 days was lower in the low-dose lamifiban plus heparin treatment group than in the control group (6.8% *vs*. 15.8%) (31).

An analysis of lamifiban plasma levels in relation to receptor occupancy and clinical outcome found in PARAGON A revealed a U-shaped curve; the lowest and highest concentrations of lamifiban had no benefits over control, whereas a middle concentration range (18-42 ng/ml; 80-90% receptor occupancy) showed substantial benefit (32, 33). The optimal therapeutic range is expected to be confirmed in the PARAGON B trial, which will assess the efficacy and tolerability of lamifiban in a larger cohort of patients.

The Platelet Aggregation Receptor Antagonist Dose Investigation for Reperfusion Gain in Myocardial Infarction (PARADIGM) was a multicenter, double-blind, placebo-controlled trial which included 400 patients with acute myocardial infarction (250 treated with recombinant t-PA, 150 treated with streptokinase) who were randomly assigned to receive either placebo or one of four different doses of lamifiban. Compared to placebo, treatment with lamifiban (all doses combined for the analysis) did not improve the incidence of death (2.1% *vs*. 2.6%), myocardial infarction (8.9% *vs*. 6.0%) or urgent revascularization (11.4% *vs*. 12.0%) at 30 days. Lamifiban reduced the time to steady-state reperfusion by 28%, as measured by continuous ST-segment monitoring, and increased the number of patients who achieved steady-state reperfusion within 2 h. Lamifiban treatment was associated with a higher incidence of major bleeding than placebo (3.0% *vs*. 1.7%) (34, 35).

In a meta-analysis evaluating thrombocytopenia as an important treatment-related complication with gpIIb/IIIa antagonists, lamifiban showed low potential for producing this side effect (odds ratio 0.83; 95% confidence interval 0.20-3.49). On the contrary, taking into account all compounds tested in clinical trials, gpIIb/IIIa antagonists increased the risk of thrombocytopenia by 42% (odds ratio 1.42; 95% confidence interval 1.07-1.89) (36).

Lamifiban is currently in phase III testing at Roche (37).

Manufacturer

F. Hoffmann-La Roche AG (CH).

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