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Annual Review 2002

Treatment of Hematological Disorders

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This issue of **Drugs of the Future** features the *Annual Review* dedicated to updated information on drugs under development for the treatment of hematologic disorders. The following table lists all drugs under development in this area, including those drugs that have been published in previous issues of the journal and others in preparation for publication in the journal, as well as some drugs that have been launched for an indication other than that discussed in the review.

As mentioned previously, the major objectives of the *Annual Reviews* are to provide our readers with a better understanding of the competitive environment in which companies are involved in getting their products on the market and to cover the progress of drugs through the development pipeline, with special emphasis on potential new therapeutic approaches to diseases for which no treatment is presently available, as well as improvements in current therapies.

We remind the readers that all of the information included in this Review is available in electronic format in our drug discovery portal **Integrity**.

We are confident that this new section will continue to be of interest to the readers and welcome your feedback.

J.R. Prous
Editor

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Drug	Source	Description/Indication	Phase
40SD02	Biomedical Frontiers/Sicor/Chiesi	Sickle cell anemia	I/II
		β-Thalassemia	I/II
Abciximab[1,2]	Centocor	Antiplatelet	III
Albrec™	Mitsubishi Pharma	Blood component	Prereg
Amediplase[3]	Menarini	Thrombolytic	II
Amotosalen Hydrochloride	Cerus/Baxter	Blood pathogen inactivation	Prereg
Ancestim[2]	Amgen	Aplastic anemia	I/II
Argatroban Monohydrate[1]	Texas Biotechnology/GlaxoSmithKline	Anticoagulant	L-2000
BB-10153	British Biotech	Thrombolytic	II
BIBR-1048	Boehringer Ingelheim	Anticoagulant	I/II
Bivariludin[2]	The Medicines Co./Innovex	Heparin-induced thrombocytopenia	III
BX-807834/CI-1031	Schering AG/Pfizer	Anticoagulant	II
Clopidogrel Hydrogensulfate[1,2]	Bristol-Myers Squibb	Antiplatelet	III
Coagulin-B	Avigen	Hemophilia B	I/II
Code-7228	Advanced Magnetics	Iron replacement	II
CS-747[1]	Sankyo/Lilly	Antiplatelet	I
CTC-111	Teijin/Chemo-Sero Ther. Res. Inst.	Anticoagulant	L-2001
Cyplex™	Cypress Bioscience	Blood substitute	II
DAC:TI	ConjuChem	Anticoagulant	I/II
Darbepoetin Alfa[1]	Amgen/Kirin Brewery	Hematopoietic	L-2001
Decitabine[1]	SuperGen	Myelodysplastic syndrome	III
		Sickle cell anemia	I/II
Deligoparin Sodium[3]	Opocrin	Anticoagulant	II
Desmoteplase	PAION	Thrombolytic	II/III
DPC-423	Bristol-Myers Squibb	Anticoagulant	I
DPC-906	Bristol-Myers Squibb	Anticoagulant	II
DX-9065a[1]	Daiichi Pharm.	Anticoagulant	II
Dynepo™	Transkaryotic Therapies/Aventis Pharma/ Cell Genesys	Anemia	Rec Approv
Ecraprost	Mitsubishi Pharma	Antiplatelet	III
FKK-138	Fujisawa	Thrombolytic	II
Flocor™	CytRx	Sickle cell anemia	III
Fondaparinux Sodium[4]	Organon/Sanofi Synthélabo	Anticoagulant	L-2002
FVX-673	Aventis Pharma	Anticoagulant	Clinical
Gantofiban	Merck KGaA/Yamanouchi	Antiplatelet	II
GH-9001	GlycoDesign/Leo	Anticoagulant	I
GW-473178	GlaxoSmithKline	Anticoagulant	I
Hematrol™	InKine	Idiopathic thrombocytopenic purpura	III
Hemoglobin Raffimer[3]	Hemosol	Blood substitute	Prereg
Hemopure™	Biopure	Blood substitute	Reg-2001
HemoZyme	SynZyme	Blood substitute	III
ICA-17043	ICAgen	Sickle cell anemia	I
ICL-670A	Novartis	β-Thalassemia	II
IDEC-131	IDEC/Eisai	Idiopathic thrombocytopenic purpura	II
Idraparinux Sodium[3]	Sanofi-Synthélabo/Organon	Anticoagulant	II
JTV-803	Japan Tobacco	Anticoagulant	II
Lanoteplase[1]	Suntory/Zeria	Thrombolytic	Prereg
LB-30870	LG Chem	Anticoagulant	Clinical
Leucotropin	Cangene	Hematopoietic	III
Liprostin	Endovasc	Antiplatelet	II

Continued

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Drug	Source	Description/Indication	Phase
LJP-1082	La Jolla Pharmaceuticals	Antibody-mediated thrombosis	I/II
MARstem	Maret	Hematopoietic	I
MaxAdFVIII	GenStar/Baxter	Hemophilia A	I
MCC-977	Mitsubishi Pharma	Anticoagulant	I
MDX-33[1]	Medarex/Aventis	Idiopathic thrombocytopenic purpura	II
Melagatran[1]	AstraZeneca	Antiplatelet	III
Monteplase[2]	Eisai	Thrombolytic	III
MR-33	Mochida/Nippon Chemical Research	Anticoagulant	Prereg
NCX-4016[1]	NicOx	Antiplatelet	I
Neulasta™	Amgen	Febril neutropenia	Reg-2002
NIX-0699	NIPRD	Sickle cell anemia	III
NM-702	Nissan Chemical/Mitsubishi Pharma	Antiplatelet	II
NS-3728	NeuroSearch	Sickle cell anemia	I
Oral Heparin/SNAC[1]	Emisphere/Bristol-Myers Squibb	Anticoagulant	III
Oral Heparin/SNAD	Emisphere/Bristol-Myers Squibb	Anticoagulant	I
Oxygent™	Alliance/Baxter	Blood substitute	III
Pamicogrel[1]	Kanebo/Torii	Antiplatelet	Prereg
PEG-Sak	ThromboGenics	Thrombolytic	II
PentaLyte™	BioTime	Blood plasma volume expander	I
PLD-117	Pliva/Receptron	Chemotherapy-induced thrombocytopenia	I
PolyHeme™	Northfield Laboratories	Blood substitute	Prereg
PT-100	Point Therapeutics	Chemotherapy-induced neutropenia	I/II
R744	Roche	Hematopoietic	II
Reviparin Sodium[2]	Knoll	Anticoagulant	III
RF-1010	SuperGen	Aplastic anemia	I
Rituximab[2]	Genetech/IDEC	Idiopathic thrombocytopenic purpura	III
rNAPc2[3]	Corvas	Anticoagulant	II
Roxifiban Acetate[1]	Bristol-Myers Squibb	Antiplatelet	III
r-ProUK	Abbott	Thrombolytic	III
rPSGL-Ig[3]	Genetics Institute	Thrombolysis enhancer	II
S-18886	Servier	Antiplatelet	Clinical
S-303	Cerus/Baxter	Blood pathogen inactivation	III
SB-249417	GlaxoSmithKline	Anticoagulant	I
SB-251353	GlaxoSmithKline	Chemotherapy-induced cytopenia	I
SL-65.0472	Sanofi-Synthélabo	Antiplatelet	I
SUN-C5174	Suntory	Antiplatelet	II
SY162	ThromboGenics	Thrombolytic	II
TA-993	Tanabe Seiyaku	Antiplatelet	II
Tenecteplase[2]	Genentech/Boehringer Ingelheim/Roche/ Schering Plough	Thrombolytic	III
ThromboSol	LifeCell	Platelet cryopreservative	Clinical
Tifacogin	Chiron/Pharmacia	Anticoagulant	III
TKT-factor VIII	Transkaryotic Therapies	Hemophilia A	I
TRI-50b	Trigen	Anticoagulant	II
Urokinase alfa	Abbott	Thrombolytic	II
VTR-PHP	VitaResc Biotech	Blood substitute	III
vWF SD-35-DH	INSERM	Hemostatic	III
Ximelagatran[1]	AstraZeneca	Antiplatelet	III
YM-337	Yamanouchi	Antiplatelet	II
Z-335	Zeria	Antiplatelet	II

Drugs in bold are covered in the Review. [1]Previously published in Drugs of the Future. [2]Launched for another indication. [3]In preparation for Drugs of the Future. [4]Monograph published in this issue.

Abciximab

Abciximab (ReoPro®) is a multireceptor inhibitor of gpIIb/IIIa, αvβ3 and MAC-1 derived from a monoclonal antibody, c7E3 Fab, that prevents blood clots by targeting and binding to the gpIIb/IIIa receptor and inhibiting platelet aggregation. Abciximab is currently indicated as an adjunct to percutaneous coronary intervention (PCI) for the prevention of cardiac ischemic complications in patients undergoing PCI and in patients with unstable angina not responding to conventional medical therapy when PCI is planned within 24 h. The product is marketed by Centocor and Lilly.

According to updated practice guidelines on the management of unstable angina and non-S-T segment elevation myocardial infarction (NSTEMI) recently issued by the American College of Cardiology (ACC) and the American Heart Association (AHA), available on the respective web sites (www.acc.org, www.americanheart.org), abciximab, which played a prominent role in the previous guidelines, has now been ruled out except in patients having an invasive procedure such as balloon angioplasty or stenting (1).

The large, international, randomized, open-label phase III GUSTO V (Global Use of Strategies To open Occluded coronary arteries) trial, overseen by the Cleveland Clinic Cardiovascular Coordinating Center (C5), compared the effects of reteplase (Retavase®, Rapilysin®) alone with those of reteplase plus abciximab in 16,588 patients with acute myocardial infarction (MI). Mortality at 30 days, the primary study endpoint, was equivalent for both treatment strategies (5.9% for reteplase alone and 5.6% for combination therapy). Combination therapy led to a 34% reduction in the recurrence of heart attack (3.5% for reteplase alone *vs.* 2.3% for combination therapy). In addition, the combined death or second heart attack rate showed a 17% reduction with combination therapy (8.8% for reteplase alone *vs.* 7.4% for combination therapy). Patients receiving combination therapy also showed reductions in other nonfatal complications, such as recurrent ischemia and severe arrhythmias, as well as in the need for PCI in the first 6 h after treatment. The incidences of intracranial hemorrhage and nonfatal disabling stroke were similar in both groups. However, combination therapy led to a higher rate of nonintracranial hemorrhage, transfusion rate and thrombocytopenia, although procedure-related bleeding was similar in both groups during PCI. Based on the results of this study, the researchers concluded that combined fibrinolytic therapy and platelet gpIIb/IIIa inhibition led to a consistent reduction in important secondary complications of MI, although these benefits were partially counterbalanced by the greater incidence of nonintracranial bleeding complications (2).

A study involving 186 patients undergoing PCI receiving aspirin and ticlodipine or clopidogrel at the time of catheterization, of whom 98 received abciximab and ticlopidine or clopidogrel for 14 days post-PCI, reported that women displayed an earlier and more pronounced increase in platelet counts following PCI as compared to men. This increase correlated with an increase in TRAP-induced platelet aggregation observed 7 and 14 days after PCI, although turbidimetric platelet aggregation was similar in both men and women (3) (Table I).

A randomized study involving 29 patients with angina pectoris scheduled for coronary intervention compared the *ex vivo* antiplatelet effects of a clopidogrel loading dose with abciximab and ticlopidine. Patients received aspirin and were randomized to 1 of 3 groups: clopidogrel 450 mg prestent + 75 mg poststent; abciximab prestent + ticlopidine 500 mg poststent; and ticlopidine 500 mg poststent. Clopidogrel and abciximab significantly suppressed the enhanced platelet activation seen during coronary intervention. Inhibition of ADP-induced platelet aggregation was significantly more complete with abciximab before and after coronary intervention. Only 1 case of bleeding and 1 case of MI were observed in the abciximab group (4).

Analysis of pooled data from several major clinical trials showed a consistent positive impact for abciximab when combined with PCI. The primary analysis was based on 3-year mortality data from 3 double-blind, placebo-controlled trials involving 5799 patients, 3355 of whom received a bolus plus 12-h infusion of abciximab with balloon angioplasty or stent placement. The data were pooled from the following trials, the results of which have been published separately: EPIC (Evaluation of c7E3 to Prevent Ischemic Complications), EPILOG (Evaluation of PTCA to Improve Long-term Outcome with abciximab GPIIb/IIIa blockade) and EPISTENT (Evaluation of IIb/IIIa Platelet Inhibitor for sTENTing). Three years after treatment, the mortality rate of the patients randomized to receive abciximab was 5.0% compared with 6.3% for those randomized to receive placebo. A secondary analysis examined the effect of abciximab on mortality using all follow-up information available for each trial. The minimum follow-up goal was 7 years for EPIC, 4.5 years for EPILOG and 3 years for EPISTENT. For each trial, there was a consistent trend for mortality reduction in patients randomized to receive abciximab: EPIC – 17.3% on abciximab *vs.* 20.1% on placebo; EPILOG – 8% on abciximab *vs.* 9.6% on placebo; EPISTENT – 3.3% on abciximab *vs.* 4.6% on placebo. Data from the analysis also indicate that the use of abciximab with a coronary procedure is cost-effective (5).

A study involving 299 patients undergoing PCI treated with aspirin (325 mg) and tirofiban (0.4 μg/kg/min for 30 min followed by 0.1 μg/kg/min for 12-24 h) or abciximab (0.25 mg/kg by bolus followed by 10 μg/min by continuous infusion for 12 h) showed that a preprocedural clopidogrel loading dose (300 mg followed by 75 mg/day for 1 month) was safe and effective in reducing major

Table I: Clinical studies of abciximab.

Indication	Design	Treatments	n	Conclusions	Ref.
Angioplasty	Comparative	Ticlopidine + Aspirin (before PCI) → Ticlopidine + Abciximab x 14 d (after PCI) (n = 39) Clopidogrel + Aspirin (before PCI) → Clopidogrel + Abciximab x 14 d (after PCI) (n = 59)	98	Abciximab in combination with ticlopidine or clopidogrel induced an increase in platelet counts in patients undergoing percutaneous coronary intervention	3
Angioplasty	Retrospective	Clopidogrel (pretreatment x 5 d or 300 mg (before PCI) + Abciximab (0.25 mg/kg bolus → 10 μg/min x 12 h) or Tirofiban (0.4 μg/kg/min x 30 min → 0.1 μg/kg/min x 12-24 h) + Aspirin + Heparin → Clopidogrel 75 mg/d x 1 mo Clopidrogel, 300 mg (after PCI) + Abciximab (0.25 mg/kg bolus → 10 μg/min x 12 h) or Tirofiban (0.4 μg/kg/min x 30 min → 0.1 μg/kg/min x 12-24 h) + Aspirin + Heparin → Clopidogrel 75 mg/d x 1 mo	299	Clopidogrel pretreatment before angioplasty in patients receiving abciximab or tirofiban in addition to aspirin was safe and effective in reducing in-hospital major adverse events	6

adverse cardiac events (Q wave or non-Q wave MI, urgent revascularization, in-hospital cardiovascular death following coronary procedure) from 14% to 5.5%; treatment did not significantly affect the rate of clinical adverse events (hemorrhage, thrombocytopenia) (6) (Table I).

Data from 34 patients with acute coronary syndrome showed that of the 10 who were administered abciximab (0.25 mg/kg by bolus followed by 0.125 μg/kg/min over 12 h), 5 achieved a response, *i.e.*, a significant decrease in CD62P expression and a concomitant significant increase in mean platelet component concentration (MPC). Of the 23 patients receiving clopidogrel (300 mg p.o.), 9 achieved a response (7).

1. *New guidelines for unstable angina and NSTEMI Rx*. DailyDrugNews.com (Daily Essentials) March 18, 2002.

2. *Reperfusion therapy for acute myocardial infarction with fibrinolytic therapy or combination reduced fibrinolytic therapy and platelet glycoprotein IIb/IIIa inhibition: The GUSTO V randomised trial*. Lancet 2001, 357(9272): 1905.

3. Arora, U.K., Mathew, S., Mascelli, M.A., Maresh, K., Kleiman, N.S. *Increase in platelet count after percutaneous coronary intervention utilizing thienopyridines and abciximab: Impact of gender*. Circulation 2001, 104(17, Suppl. 2): Abst 1659.

4. Claeys, M.J., Van der Plancken, M.G., Michiels, J.J., Vertessen, F., Dilling, D., Bosmans, J.M., Vrints, C. *Comparison of antiplatelet effect of loading dose of clopidogrel versus abciximab during coronary intervention*. Thromb Haemost 2001, (Suppl.): Abst P3087.

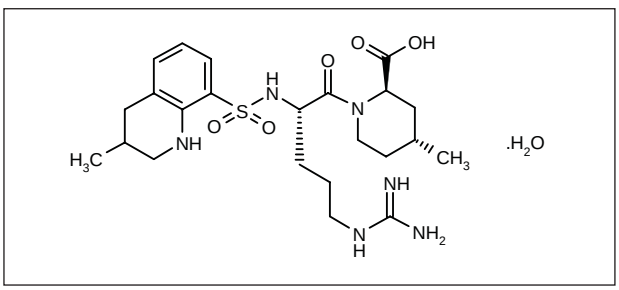
5. *ReoPro has consistent benefits in reducing the risk of death when combined with PCI*. DailyDrugNews.com (Daily Essentials) March 28, 2001.

6. Assali, A.R., Salloum, J., Sdringola, S. et al. *Effects of clopidogrel pretreatment before percutaneous coronary intervention in patients treated with glycoprotein IIb/IIIa inhibitors (abciximab or tirofiban)*. Am J Cardiol 2001, 88(8): 884.

7. Ahnadi, C.E., Boughrassa, F.F., Poisson, V. et al. *Platelet activation variability in patient response to abciximab and clopidogrel*. Blood 2001, 98(11, Part 2): Abst 3773.

Original monograph - Drugs Fut 1995, 20(5): 457.

Argatroban Monohydrate



Argatroban is the first synthetic direct thrombin inhibitor approved for the prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia (HIT).

Argatroban was approved for this indication by the FDA in late 2000, and last year in Canada, although it was first approved as a treatment for ischemic stroke in 1996 in Japan, where it is marketed by Mitsubishi Pharma. GlaxoSmithKline is marketing the drug for HIT through an agreement with Texas Biotechnology, which licensed rights to argatroban in 1993 and has been the primary developer of the drug for HIT. Argatroban is also being evaluated in several different cardiovascular indications, *e.g.*, in combination with gpIIb/IIIa inhibitors for patients undergoing percutaneous coronary intervention (PCI) and in ischemic stroke (1-3).

An sNDA has been filed seeking FDA approval for use in patients who have or who are at risk of developing HIT and who are undergoing PCI. At the annual meeting of

the American College of Chest Physicians (ACCP), data were reported from 3 clinical trials which showed that argatroban provided adequate anticoagulation in patients undergoing coronary interventions who had developed thrombotic complications after prior exposure to heparin. In a combined analysis of the studies, of the 91 patients treated with argatroban, 97.8% had adequate anticoagulation, while 94.5% achieved satisfactory procedural outcomes. In patients who received argatroban, acute procedural success was 98.9% *versus* 94.3% in the control group. Similarly, major bleeding rates for argatroban patients compared favorably with historical controls (2.2% *vs.* 3.1%). Data evaluating the efficacy of argatroban in HIT patients who required PCI on multiple occasions were also reported. In this analysis, outcomes from the 91 patients who received initial treatment with argatroban during PCI were compared with outcomes from patients who had multiple procedures and multiple exposures to argatroban therapy. Results from this analysis demonstrated that 100% of the 21 patients achieved satisfactory procedural outcomes and acute procedural success. All of these patients also experienced adequate anticoagulation upon reexposure to argatroban, without major bleeding. Repeated argatroban exposure was well tolerated, without an increase in safety risk (4).

Texas Biotechnology and Mitsubishi Pharma are funding a multicenter, placebo-controlled phase II trial (ARGIS-I) to evaluate the safety and efficacy of intravenous infusion of argatroban in patients with acute ischemic stroke. The trial is the first of its kind in the U.S. to evaluate the use of a direct thrombin inhibitor as a treatment for ischemic stroke. As a direct inhibitor of thrombin, including clot-bound thrombin, argatroban may influence both the primary clot, as well as the collateral and microcirculation of the brain in and around the original infarction. As a result of this mechanism of action, argatroban may prevent additional clots from forming. This effect was seen in patients in phase III trials for HIT where a reduction in secondary thrombus formation following initiation of argatroban was reported (5).

Results from a preclinical study demonstrated that coadministration of argatroban and tPA (tissue-type plasminogen activator) was associated with reduction in ischemic lesion size without an increase in gross cerebral hemorrhage in a rat model of embolic stroke (6).

The pharmacokinetics of argatroban were determined in a porcine model of cardiopulmonary bypass and compared to those in normal pigs. In normal pigs, argatroban was administered as an initial bolus of 7.5 mg/kg and a second dose if activated clotting time was below 300 s, followed by continuous infusion of 60 μg/kg/min for 60 min. In the bypass model, argatroban 7.5 mg was administered prior to cannulation and followed by 7.5 mg/kg into the pump prime. Administration of an additional 15 mg/kg was given at the rate of 60 μg/kg/min. The results suggested that circulating argatroban at 15-20 μg/ml is sufficient for cardiopulmonary bypass surgery, which is easily achieved (7).

Argatroban and its major metabolite were added at 25 μg/ml to human plasma, cerebrospinal fluid and urine samples from donors. Both the drug and its metabolite were found to be stable in these fluids, indicating that the pharmacokinetics and pharmacodynamics can be determined in a variety of biological fluids (8).

The effects of argatroban (6.25 μg/kg/min for 48 h), human recombinant tPA (10 mg/kg over 30 min following an initial 10% bolus) and combination of the agents, given via the femoral vein starting 4 h after middle cerebral artery occlusion, have been examined in a rat model of embolic focal cerebral ischemia. Compared to untreated controls, argatroban- and tPA-treated animals which showed respective mean ischemic lesion sizes of 35.3%, 36.5% and 43.4%, lesion size in the rats treated with the combination was significantly reduced to 17.1%. Importantly, gross cerebral hemorrhage was not increased (20%, 17%, 33% and 17%, respectively, in control, argatroban, tPA and argatroban + tPA groups). These findings indicate that combination of argatroban with tPA in acute stroke may widen the therapeutic window for the safe administration of tPA (9).

To examine the effect of their interactions on activated clotting time, argatroban alone 0-10 μg/ml and in combination with tirofiban 5 μg/ml was profiled in 6 healthy volunteers. A synergistic reaction was seen regarding the anticoagulant effect, which was confirmed in a further study in patients with HIT (10).

Anticoagulation with argatroban was assessed in 14 patients with HIT undergoing PCI. The agent was administered as an initial bolus dose of 350 μg/kg followed by an infusion of 25 μg/kg/min during the procedure. The investigators found that the anticoagulant effect of argatroban could be monitored using the Heparin Management Test, Ecarin Clotting Time, celite Activated Clotting Time and kaolin-activated ACT (11).

Data from 2 clinical trials in a total of 809 patients with HIT treated with argatroban were analyzed for factors influencing outcome. The severity of the thrombocytopenia was the best predictor of death, thrombotic progression and amputation. It was also found that patients who had had cardiovascular surgery were more likely to have limb loss and those with renal failure were more likely to die (12).

A review of clinical trial records of 304 patients with HIT who were treated with argatroban revealed that 165 of them were transferred to warfarin. Without specific monitoring guidelines, physicians were able to transfer these patients from argatroban to warfarin anticoagulation with acceptable rates of thrombotic and hemorrhagic complications (13).

The efficacy of argatroban (0.5 μg/kg/min initially, increased to 1 mcg/kg/min and then tapered according to results of activated partial thromboplastin time [aPTT) monitoring) as a treatment for HIT was demonstrated in the case of a 45-year-old woman with stage IB endometrial cancer who developed pulmonary embolism after undergoing total abdominal hysterectomy, bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The

Table II: Clinical studies of argatroban.

Indication	Design	Treatments	n	Conclusions	Ref.
Heparin-induced thrombocytopenia	Pooled data	Study I: Healthy volunteers Argatroban 0 μg/ml → + Tirofiban, 5 μg/ml Argatroban 2.5 μg/ml → + Tirofiban, 5 μg/ml Argatroban 5 μg/ml → + Tirofiban, 5 μg/ml Argatroban 10 μg/ml → + Tirofiban 5 μg/ml Study II: Heparin-induced thrombocytopenia patients Argatroban, 300 μg/kg iv bolus → Argatroban, 10 μg/kg/min iv infusion + Tirofiban, 10 μg/kg → 0.015 μg/kg/min iv infusion		Results showed a synergistic reaction between argatroban and tirofiban in regard to the anticoagulant effect	10
Heparin-induced thrombocytopenia	Retrospective	Argatroban, 2 μg/kg/min (adjusted to aPTT 1.5-3.0) (n = 812) Historical controls (standard care or anticoagulation) (n = 193)	1005	Argatroban was safe and effective in decreasing mortality and preventing acute ischemic stroke in heparin-induced thrombocytopenia	15
Heparin-induced thrombocytopenia	Pooled data	Argatroban, 2 μg/kg/min iv (adjusted to aPTT 1.5-3.0)		Argatroban was safe and effective in patients with previous diagnosis of heparin-induced thrombocytopenia who required anticoagulation	18
Heparin-induced thrombocytopenia	Multicenter, open	Argatroban, 2 μg/kg/min iv (adjusted to aPTT 1.5-3.0) x 14 d	497	Treatment with argatroban was effective in lowering mortality rate from thrombosis and preventing new fibrinolytic events in patients with heparin-induced thrombocytopenia, without increasing bleeding risk	19

patient was treated with heparin, which resulted in thrombocytopenia and central vein catheter-related thrombosis requiring thrombectomy. Argatroban was administered during and after thrombectomy and, after tapering of the agent, oral warfarin (1.2 mg/day) and aspirin (81 mg/day) were administered. Platelet counts recovered to 104,000 and 236,000 per μl, respectively, on day 1 and 4 after thrombectomy (14).

The effects of argatroban on neurological complications were evaluated in over 1000 patients with HIT. Patients (n = 812) treated with argatroban (2 μg/kg/min) were compared to historical controls (n = 193) receiving standard of care. Retrospective analysis revealed significantly lower stroke-associated mortality in patients treated with argatroban compared to controls (1.0% *vs.* 3.1%). Also, its safety was indicated by a lack of intracerebral hemorrhage (15).

Argatroban was successfully used as an anticoagulant in a patient with severe acquired antithrombin III deficiency resulting from extensive burn injuries, and in whom treatment with heparin failed (16).

Lepirudin and argatroban produced benefits in 5 patients with disseminated intravascular coagulation in the presence of suspected heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) (17).

An analysis of 3 clinical trials was undertaken to compare outcomes in patients with a history of HIT who were no longer thrombocytopenic and required anticoagulation (n = 87) to patients with active HIT (n = 725). All patients were treated with i.v. argatroban begun at 2 μg/kg/min. Argatroban was found to be a safe and effective anticoagulant in patients with latent HIT and these patients had fewer adverse outcomes than those with active HIT (18).

Argatroban treatment was assessed in a trial in 160 patients with HIT and 144 with HITTS. Study subjects were given i.v. argatroban 2 μg/kg/min in order to maintain aPTT at 1.5-3 times the baseline value, for an average of 6 days. Compared with 147 historical control subjects with HIT, argatroban improved clinical outcomes and did not increase the risk of bleeding (19).

Results of some of the clinical studies of argatroban are summarized in Table II.

1. *Texas Biotechnology receives approvable letter from FDA for expanded argatroban indication*. DailyDrugNews.com (Daily Essentials) July 23, 2001.

2. *Texas Biotechnology announces approval of argatroban in Canada*. DailyDrugNews.com (Daily Essentials) Aug 3, 2001.

3. *Phase II trial of Argatroban plus gpIIb/IIIa antagonists initiated in patients undergoing PCI*. DailyDrugNews.com (Daily Essentials) Oct 10, 2001.

4. *Argatroban sNDA filed for HIT patients undergoing PCI*. DailyDrugNews.com (Daily Essentials) Jan 10, 2001

5. *Argatroban enters phase II for ischemic stroke*. DailyDrugNews.com (Daily Essentials) March 16, 2001.

6. *Promising preclinical data reported for argatroban in rat ischemic stroke model*. DailyDrugNews.com (Daily Essentials) May 10, 2001.

7. Ahmad, S., Rusterholtz, I., Jain, S. et al. *Anticoagulant dosage optimization of argatroban in a porcine model of cardiopulmonary bypass surgery*. Blood 2001, 98(11, Part 1): Abst 191.

8. Daud, A.N., Ahmad, S., Walenga, J.M., Lewis, B.E., Mayuga, M., Fareed, J. *Matrix influence and protein binding of the biochemical profile of argatroban and its metabolite (M1): Potential clinical implications*. Clin Chem 2001, 47(6, Suppl.): Abst 519.

9. Morris, D.C., Zhang, L., Zhang, Z.G., Berens, K.L., Brown, P.M., Chopp, M. *Opening the window of opportunity for treatment of stroke with argatroban and tPA*. Acad Emerg Med 2001, 8(5): 541.

10. Iqbal, O., Lewis, B.E., Ahmad, S., Hoppensteadt, D.A., Leya, F., Fareed, J. *Dosage adjustment of argatroban justified in combination with glycoprotein IIb/IIIa receptor antagonist: Laboratory and clinical implications*. Blood 2001, 98(11, Part 1): Abst 195.

11. Iqbal, O., Ahmad, S., Lewis, B.E., Mousa, Y., Demir, M., Hoppensteadt, D.A., Fareed, J. *Monitoring of the anticoagulant effects of argatroban in patients with heparin-induced thrombocytopenia undergoing percutaneous coronary interventions – The ARG 310 study*. Clin Chem 2001, 47(6, Suppl.): Abst 554.

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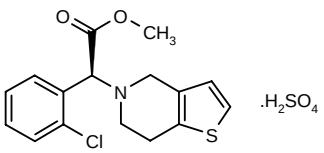
Clopidogrel Hydrogensulfate



The FDA recently approved the use of the antiplatelet therapy clopidogrel hydrogensulfate (clopidogrel bisulfate, Plavix®, Iscover®) for the new indication of acute coronary syndrome, defined as unstable angina and non-Q wave myocardial infarction (MI). Clopidogrel is already approved for reducing atherosclerotic events in patients with a history of recent heart attack, recent stroke or established peripheral arterial disease and is marketed worldwide by Sanofi-Synthélabo and Bristol-Myers Squibb (1, 2).

An update to practice guidelines on the management of unstable angina and non-S-T segment elevation myocardial infarction (NSTEMI) was recently released from the American College of Cardiology (ACC) and the American Heart Association (AHA) and is available on their respective web sites (www.acc.org, www.americanheart.org). Clopidogrel hydrogensulfate was recommended in addition to aspirin and heparin in nearly all patients with unstable angina and NSTEMI (3).

Experiments in CHO cells transfected with the human $P2Y_{12}$ receptor showed that the receptor is antagonized by the active metabolite of clopidogrel (4).

In an arteriovenous shunt model in rabbits, administration of clopidogrel 5 mg/kg in combination with SR-121787 10 mg/kg decreased thrombus weight. The combination of clopidogrel 5 mg/kg and SR-121787 20 mg/kg also decreased thrombus weight, but with a greatly reduced risk of bleeding (5).

Using a pig model of coronary artery thrombus formation or cyclic flow reductions (CFR), the antithrombotic effect of clopidogrel (0.1 or 5 mg/kg), aspirin (1 or 7 mg/kg) and a low-dose combination of the two agents (0.1/1 mg/kg clopidogrel/aspirin) administered 30 min after establishing CFR was demonstrated. Significant reductions in CFR frequency were observed at 60 min with 7 mg/kg aspirin (–48%) and at 120 min with 5 mg/kg clopidogrel (–65%), but not with the low doses of either agent. However, significant, rapid and enhanced abrogation of CFR (–70%) was observed at 90 min with the low-dose combination (6).

A randomized study examined the effects of a gpIIIa polymorphism (PLA2) on the platelet-inhibitory effects of clopidogrel (75 mg/day) and aspirin (325 mg/day), alone and in combination, in 30 PLA1/1 and 30 PLA1/2 patients with coronary heart disease. Platelet aggregation experiments performed 10 days later showed that aspirin was significantly more active than clopidogrel in inhibiting both epinephrine- and collagen-stimulated platelets, but clopidogrel was significantly more active in inhibiting ADP-stimulated platelets. Enhanced inhibition of ADP-stimulated platelets was observed with combination treatment. ADP-stimulated platelets obtained from PLA1/2 donors were inhibited to a significantly greater extent than those from PLA1/1 donors (7).

A study involving 52 patients with coronary artery disease (CAD) undergoing stent implantation and 20 control patients who were monitored for 2 days before coronary intervention compared the effects of clopidogrel as loading doses of 300 and 450 mg followed by 75 mg/day on P-selectin expression. On days 1 and 2 prior to stenting, the higher loading dose caused a significantly greater reduction in inducible P-selectin expression in ADP-stimulated platelets as compared to the lower loading dose. Plasma P-selectin levels were unaffected by treatment (8).

A randomized study in 30 patients undergoing coronary stent replacement showed the superior efficacy of a high loading dose (600 mg) of clopidogrel followed by 150 mg/day over a low loading dose of clopidogrel (300 mg) followed by 75 mg/day and ticlopidine (2 x 500 mg loading dose followed by 500 mg/day) in suppressing poststenting platelet aggregation. In addition, the high loading dose of clopidogrel accelerated inhibition of ADP-stimulated platelet aggregation within a few hours of dosing; similar inhibition with the 300-mg loading dose was only seen 48 h postdosing (9).

Within 24 h of symptom onset, 12,562 patients with acute coronary syndrome without S-T segment elevation were randomized to aspirin plus clopidogrel (300 mg immediately, then 75 mg once daily) or aspirin plus placebo for 3-12 months. Clopidogrel had a beneficial effect in preventing death from cardiovascular causes, nonfatal myocardial infarction and stroke, but increased the risk of major bleeding (10). The results of this study and several other studies described below are summarized in Table III.

The results from a study in 100 patients undergoing elective stent placement who received aspirin (81-325 mg/daily for at least 1 week prior to stenting) showed that a loading dose of clopidogrel (300 mg) 3-24 h before coronary stenting was more effective in significantly inhibiting ADP- and collagen-stimulated platelet aggregation than a dose of 75 mg given at the time of intervention. None of the patients in this study developed stent thrombosis. The clopidogrel loading dose also significantly decreased collagen-induced whole blood aggregation and shear-induced closure time, but had no effect on contractile force. A significant enhancement in gpIIb/IIIa expression and a reduction in PECAM-1 and CD107a expression were seen in those patients receiving the loading dose of clopidogrel, but not in those receiving 75 mg at the time of intervention. The loading dose also inhibited the increase in platelet activity observed 2 h and 2 days poststenting. Treatment with clopidogrel for 5 days resulted in marked inhibition of gpIb, PECAM-1, CD107a and gpIIb/IIIa (11, 12).

A report analyzing data from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) trial concluded that the efficacy of clopidogrel plus aspirin seen in cardiac patients cannot be extrapolated to cerebrovascular patients due to the differences between these types of patients (13).

The efficacy of a high loading dose of clopidogrel prior to coronary stenting was demonstrated in a study including 864 patients administered the agent (600 mg 2-4 h before intervention followed by 150 mg/day until discharge and 75 mg/day until day 28 poststenting) as compared to 870 ticlopidine-treated patients (62% of the patients were also receiving abciximab). The primary endpoint was composite death, myocardial infarction and urgent revascularization after 30 days. Clopidogrel-treated patients (with or without abciximab treatment) experienced a 35% reduction in the risk of the primary endpoint. There were no significant differences in the severity of thrombocytopenia and incidence of bleeding complications between groups (14, 15).

A preliminary fact-finding study enrolling 54 patients who underwent a total of 76 peripheral arterial bypass operations has compared the efficacy of clopidogrel (75 mg once daily) with aspirin (300 mg once daily) on long-term synthetic graft patency. Clopidogrel was as effective as aspirin in terms of rates of graft patency (84 and 81%, respectively) and mean time to graft occlusion (5.5 ± 1.7 and 8.4 ± 4.6 months, respectively). However, more adverse effects were seen in the group receiving aspirin (nausea, vomiting, diarrhea, rash and bleeding) as compared to the clopidogrel group (1 case of diarrhea and 1 case of nausea and vomiting) (16).

A prospective study using *ex vivo* blood samples from 30 patients with stable angina pectoris and abnormal stress tests who had undergone elective percutaneous coronary angioplasty and stenting compared the effects of combined therapy including aspirin (100 mg b.i.d. p.o.) and clopidogrel (75 mg/day or 450 mg before stenting followed by 75 mg/day) or ticlopidine (500 mg b.i.d. on the day of stenting and 250 mg b.i.d. thereafter) on platelet function. Treatment with 450 mg clopidogrel followed by 75 mg/day was significantly faster and superior to standard clopidogrel (75 mg/day) or ticlopidine therapy in inhibiting ADP-induced platelet aggregation. The accelerated antiplatelet activity observed when a loading dose of clopidogrel was administered suggests that the agent may be effective for high-risk patients undergoing coronary stenting (17).

A possible interaction of celecoxib (200 mg/day) and clopidogrel (75 mg/day) via CYP2C9 has been shown in a case involving an 86-year-old woman with an episode of syncope associated with complete heart block and osteoarthritis. The patient suffered intracerebral hemorrhage following short-term concomitant treatment with the agents. It was concluded that older subjects may have a higher hemorrhagic risk with concomitant clopidogrel and celecoxib treatment (18).

A study involving 34 patients with acute coronary syndrome showed that of the 23 patients receiving clopidogrel (300 mg p.o.), 9 achieved a response (*i.e.*, significant decrease in CD62P expression and a concomitant significant increase in mean platelet component concentration [MPC]). Clopidogrel had no effect on MPC levels or

Table III: Clinical studies of clopidogrel hydrogensulfate

Indication	Design	Treatments	n	Conclusions	Ref.
Coronary revascularization	Randomized, double-blind, multicenter	Clopidogrel, 300 mg/d po sd → Clopidogrel, 75 mg/d po + Aspirin, 75-325 mg/d x 3-12 mo Placebo + Aspirin, 75 325 mg/d x 3-12 mo	12,562	Clopidogrel plus aspirin reduced the risk of death from cardiovascular causes, nonfatal myocardical infarction or stroke as well as related ischemic events, but increased the risk of major bleeding in patients with acute coronary syndrome without S-T segment elevation	10
Coronary revascularization		Ticlopidine + Aspirin (before PCI) → Ticlopidine + Abciximab x 14 d (after PCI) (n = 39) Clopidogrel + Aspirin (before PCI) → Clopidogrel + Abciximab x 14 d (after PCI) (n = 59)	98	Abciximab in combination with ticlopidine or clopidogrel produced an increase in platelet counts in patients undergoing percutaneous coronary intervention	22
Coronary revascularization	Retrospective	Clopidogrel (pretreatment x 5 d or 300 mg before PCI) + Abciximab (0.25 mg/kg bolus → 10 μg/min x 12 h) or Tirofiban (0.4 μg/kg/min x 30 min → 0.1 μg/kg/min x 12-24 h) + Aspirin + Heparin → Clopidogrel 75 mg/d x 1 mo Clopidogel, 300 mg (after PCI) + Abciximab (0.25 mg/kg bolus → 10 μg/min x12 h) or Tirofiban (0.4 μg/kg/min x 30 min → 0.1 μg/kg/min x 12-24 h) + Aspirin + Heparin → Clopidogrel 75 mg/d x 1 mo	299	Clopidogrel pretreatment before angioplasty in patients receiving abciximab or tirofiban in addition to aspirin was safe and effective in reducing in-hospital major adverse events	30
Myocardial infarction	Randomized, double-blind, multicenter	Clopidogrel Aspirin	19,185	Clopidogrel was more effective than aspirin in reducing the risk of recurrent ischemic events, especially in the high-risk patients with prior cardiac surgery, as well as decreasing the risk of bleeding	32
Coronary revascularization	Randomized, double-blind, multicenter	Clopidogrel, 300 mg/d po + Aspirin, 75-300 mg (starting 6 d before PCI) x 3-12 mo (n = 1313) Placebo + Aspirin, 75-300 mg (starting 6 d before PCI) x 3-12 mo (n = 1345)	2658	Clopidogrel plus aspirin pretreatment and long-term follow-up was effective in reducing major cardiovascular events in percutaneous coronary intervention in patients with acute coronary syndrome	33
Coronary revascularization	Retrospective	Clopidogrel pretreatment + Aspirin Control, no pretreatment + Aspirin	860	Pretreatment with clopidogrel was effective in reducing 30-day death or acute myocardial infarction in patients with elevated baseline CRP levels undergoing coronary stenting	34
Coronary revascularization	Randomized	Aspirin + Abciximab prestent + ticlopidine, 500 mg poststent (n = 11) Aspirin + Clopidogrel, 450 mg prestent + 75 mg poststent (n = 8) Aspirin + Ticlopidine 500 mg poststent (control) (n = 10)	29	Platelet activation during coronary intervention was completely inhibited by both abciximab and clopidogrel	36
Coronary revascularization	Open, pooled data	Clopidogrel 300 mg sd (preprocedure) → Active γ-radiation + Clopidogrel, 75 mg/d po x 6 mo (n = 120) Active γ-radiation + Clopidogrel or Ticlopidine, 250 mg/d po x 1 mo (n = 125) Placebo + Clopidogrel or Ticlopidine, 250 mg/d po x 1 mo (n = 126)	371	Clopidogrel plus aspirin long-term treatment for 6 months was well tolerated and more effective in reducing the late thrombosis rate than 1 month treatment in patients with in-stent restenosis undergoing intracoronary γ-radiation	38
Unstable angina	Randomized, double-blind, multicenter	Clopidogrel, 300 mg → 75 mg/d + Aspirin, 75-300 mg/d x 3-12 mo (n = 6259) Placebo + Aspirin, 75-300 mg/d x 3-12 mo (n = 6303)	12,562	Clopidogrel was safe and reduced the risk of cardiovascular death, stroke and myocardial infarction in both high- and low-risk patients without increasing the risk of intracraneal hemorrhage	42

CD62P expression in the 14 remaining patients who had normal platelet activation prior to treatment. Of 10 patients who were administered abciximab (0.25 mg/kg bolus followed by 0.125 μg/kg/min by 12-h infusion), 5 achieved a response (19).

Results from a double-blind, randomized, placebo-controlled study including 30 patients with impaired blood rheology and atherosclerosis showed that treatment with clopidogrel (75 mg/day for 3 weeks) significantly improved blood viscosity at high shear rate, red cell filterability rates and dynamic red cell deformability index. No adverse effects were reported. Clopidogrel-induced improvements in blood viscosity and red cell aggregation were seen after 1 week of treatment and were sustained throughout the treatment period (20).

Results from a multicenter, nested case-control study in 394 patients with or without stent thrombosis reported that clopidogrel was less protective than ticlopidine against stent thrombosis. Those patients receiving clopidogrel had a significantly higher risk of developing stent thrombosis as compared to those receiving ticlopidine (21).

A study in 186 patients undergoing PCI receiving aspirin and ticlodipine or clopidogrel at the time of catheterization, of whom 98 received abciximab and ticlopidine or clopidogrel for 14 days post-PCI, reported that women displayed an earlier and more pronounced increase in platelet counts following PCI as compared to men. This increase correlated with an increase in TRAP-induced platelet aggregation observed 7 and 14 days after PCI, although turbidimetric platelet aggregation was similar in both men and women (22).

A randomized study involving 41 patients scheduled to undergo PCI compared the effects of a high (450 or 600 mg) *versus* standard (300 mg) loading doses of clopidogrel on ADP-stimulated platelet aggregation prior to PCI. Results showed that platelet aggregation was inhibited at 3 h postdosing with 300 mg and no further inhibition was noted with higher doses (23).

A trial in 31 patients with a past history of myocardial infarction or angor and receiving aspirin (375 mg) compared the antiplatelet effects of a clopidogrel loading dose (300 mg) to ticlopidine (1000 mg) administered during the acute phase of coronary stenting. Clopidogrel treatment significantly reduced platelet-bound fibrinogen and platelet-monocyte conjugates prior to ADP stimulation and significantly inhibited ADP-stimulated platelet aggregation and CD62P expression at 2.5 h postdosing; effects were comparable at 24 h postdosing. The ticlopidine loading dose only inhibited ADP-induced aggregation at 24 h postdosing (24).

Another study in 50 aspirin-treated patients undergoing elective PTCA showed that additional treatment with clopidogrel (300 mg 3 h before PTCA) resulted in antiplatelet response in 60% of the patients. However, platelet aggregation was unaffected by clopidogrel in some aspirin-treated patients. This lack of or modest antiplatelet response to clopidogrel was associated with high levels of C-peptide and catecholamines (25).

Meta-analysis of results from 20 randomized trials conducted in a total of 13,955 patients who received coronary stents showed that clopidogrel is as effective as ticlopidine but has better tolerability and fewer side effects. The pooled rates of the primary endpoint, which was 30-day major adverse cardiac events, were 2.1 and 4.04% for the clopidogrel and ticlopidine groups, respectively. The odds ratio for having an ischemic event was in favor of clopidogrel. Moreover, the rate of mortality for clopidogrel was significantly lower than for ticlopidine (0.48% *vs*. 1.09%). From the results of this analysis, it was concluded that clopidogrel plus aspirin should replace ticlopidine plus aspirin as standard antiplatelet therapy after stenting (26).

Of 162 patients who had undergone carotid artery stenting, those treated with both clopidogrel and aspirin had a significantly lower cumulative rate of 30-day death, stroke, transient ischemic attack and myocardial infarction as compared to ticlopidine (4.3% *vs*. 13%) (27).

A study conducted in 10 healthy volunteers demonstrated that inhibition of platelet function (*i.e*., ADP-stimulated CD62P expression and PAC-1 binding) seen with clopidogrel treatment (75 mg/day for 7 days) was irreversible. Complete recovery of platelet function was observed by 7 days after discontinuation of clopidogrel dosing (28, 29).

A study involving 299 patients undergoing PCI treated with aspirin (325 mg) and tirofiban (0.4 μg/kg/min for 30 min followed by 0.1 μg/kg/min for 12-24 h) or abciximab (0.25 mg/kg bolus followed by 10 μg/min continuous infusion for 12 h) showed that a preprocedural clopidogrel loading dose (300 mg followed by 75 mg/day for 1 month) was safe and effective in reducing major adverse cardiac events (Q wave or non-Q wave myocardial infarction, urgent revascularization, in-hospital cardiovascular death following coronary procedure) from 14% to 5.5%; treatment did not significantly affect the rate of clinical adverse events (hemorrhage, thrombocytopenia) (30, 31).

The ischemic event rates were determined for 1480 patients with a history of cardiac surgery who took part in a randomized study comparing antiplatelet therapy with clopidogrel and aspirin. Clopidogrel was associated with a much lower risk of recurrent ischemic events in these patients and a lower risk of bleeding (32).

In a randomized, double-blind study, 2658 patients with non-S-T elevation acute coronary syndrome undergoing PCI were assigned clopidogrel or placebo. Aspirin and study drug were given for a median of 6 days before the procedure and for a median of 10 days overall. After PCI, most patients in both groups received thienopyridine for about 4 weeks and then the study drug again for a mean of 8 months. Clopidogrel pretreatment and long-term therapy was superior in reducing major cardiovascular events as compared with placebo (33).

An analysis of patients undergoing coronary stenting and pretreated with clopidogrel showed that those

patients who had elevated baseline C-reactive protein levels had a significant reduction in 30-day death or acute myocardial infarction (34).

Doctors have reported the case of an 88-year-old man who developed fatal aplastic anemia after 5 months of clopidogrel therapy (35).

A randomized study involving 29 patients with angina pectoris scheduled for coronary intervention compared the *ex vivo* antiplatelet effects of a clopidogrel loading dose with abciximab and ticlopidine. Patients received aspirin and were randomized to 1 of 3 groups: clopidogrel 450 mg prestent + 75 mg poststent, abciximab prestent + ticlopidine 500 mg poststent, and ticlopidine 500 mg poststent. Clopidogrel and abciximab significantly suppressed the enhanced platelet activation seen during coronary intervention. Inhibition of ADP-induced platelet aggregation was significantly more complete with abciximab before and after coronary intervention (36).

Analysis of results from clopidogrel trials involving a total of 1241 patients revealed that use of the agent is associated with increased platelet transfusion rates as compared to controls. The incidence of transfusion was 11% overall and 6.4% when patients requiring urgent or elective coronary artery bypass graft were excluded. It was concluded that platelet function assays may be useful when administering clopidogrel (37).

In 120 patients with in-stent restenosis, the prevention of late thrombosis with γ-radiation, clopidogrel and aspirin prescribed for 6 months was compared with outcome data from previous studies where patients received short-term antiplatelet therapy and γ-radiation or placebo for 1 month. Treatment of patients with γ-radiation and long-term clopidogrel and aspirin was well tolerated and reduced the late thrombosis rate as compared to treatment with γ-radiation, clopidogrel and aspirin for only 1 month (38).

A study involving 50 aspirin (100 mg/day)-treated patients undergoing elective PCI (performed 24-72 h after the start of treatment) showed that a loading dose of clopidogrel (300 mg followed by 75 mg/day) inhibited ADP-stimulated platelet activation and aggregation sooner (maximum inhibition seen at 6 h postdosing) than ticlopidine (500 mg loading dose followed by 250 mg b.i.d.); the extent of inhibition was similar for both agents. Both agents also inhibited P-selectin, GP53 and PAC-1 (activated gpIIb/IIIa receptor) expression and inhibited platelet-leukocyte adhesion, although the effects were seen sooner with clopidogrel. The inhibitory effects of both agents were comparable after 7 days of treatment (39).

An analysis of the responses of 3037 patients compared the efficacy of clopidogrel with ticlopidine in improving the safety profile of stenting. Both agents were found to improve the study endpoint, which included in-hospital death, myocardial infarction and urgent revascularization (40).

Results from the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events) trial, an international, double-blind, randomized, placebo-controlled study in more than 12,500 patients with unstable angina and non-Q wave myocardial infarction, showed the efficacy of early and long-term use of clopidogrel (300 mg loading dose followed by 75 mg/day) on top of standard therapy including aspirin (75-325 mg/day). Mean treatment and follow-up duration was 9 months. Clopidogrel significantly decreased the risk of composite cardiovascular death, stroke and myocardial infarction by 20%. Clopidogrel-induced cardioprotection was observed within 2 h of treatment and was sustained at 30 days with long-term treatment. Improvement with the agent was observed in both high- and low-risk patients. The risk of bleeding was acceptable and the incidence of intracranial hemorrhage did not increase with clopidogrel treatment (41, 42).

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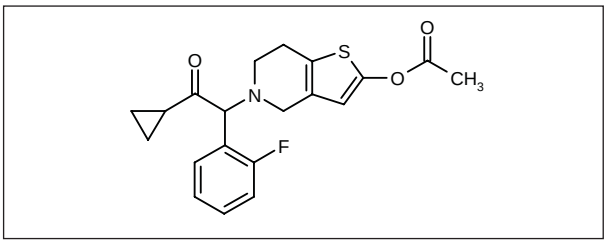
CS-747



CS-747, discovered by Sankyo and Ube, is a potent oral antiplatelet agent that blocks ADP receptors.

CS-747 is a prodrug-type thienopyridine antiplatelet agent acting as a G_i-linked P2T (P2TAC) receptor antagonist. The compound is converted in the liver to the pharmacologically active metabolite R-99224. Extensive *in vitro* and *ex vivo* profiling of CS-747 and its metabolite indicated that the P2TAC receptor-antagonist activity of orally administered CS-747 is due to R-99224. The compound is currently in phase I clinical trials, with phase II studies expected to begin this year. It will be developed for the secondary prevention of thrombotic cardiovascular complications in patients with a recent ischemic stroke or with acute coronary syndromes. CS-747 will also be developed for reducing secondary complications, including death, recurrent myocardial infarction, recurrent stroke and rehospitalization for severe angina. Lilly and Sankyo have signed an agreement to copromote the product in the U.S. For the remaining global market, Lilly and Sankyo will jointly market the product except for certain countries where Lilly will receive exclusive sales and marketing rights. Lilly and Sankyo will share in the development of the compound and plan to manufacture the finished product. Ube will manufacture the bulk material (1-3).

In rats, oral administration of CS-747 (0.3-3 mg/kg/day) for 3 days dose-dependently inhibited ADP-induced platelet aggregation with higher potency (ID_{50} = 0.54 mg/kg) than after single doses (ID_{50} = 1.2 mg/kg); clopidogrel (ID_{50} = 6.2 mg/kg) and ticlopidine (ID_{50} = 300 mg/kg) were less effective. Three-day administration of CS-747 (0.1-1 mg/kg/day) also resulted in dose-dependent inhibition of thrombus formation in a rat carotid artery thrombosis model, with a minimum effective dose of 0.3 mg/kg; again, clopidogrel and ticlopidine were less effective. The relative potency of CS-747, clopidogrel and ticlopidine for prolongation of tail bleeding time was similar to the antithrombotic/antiaggregatory effects, indicating that CS-747 has a comparable benefit/risk ratio to the reference agents (4).

Stable, orally absorbable and low-toxicity acid addition salts of CS-747 have been claimed (5).

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Darbepoetin Alfa

Darbepoetin alfa, also known as novel erythropoiesis-stimulating protein, or NESP, was launched by Amgen as ARANESPTM in the U.S. and Europe last year for the treatment of anemia associated with chronic renal failure, including patients on dialysis and patients not on dialysis. The product has also been approved in Australia (1-5).

Darbepoetin alfa is distinguished from the currently available recombinant human erythropoietin (rHuEPO), or epoetin alfa (Epogen®, Procrit®), in that it requires fewer injections and has a longer duration of action. Amgen is also seeking clearance in the U.S. and Europe to expand the clinical indications for darbepoetin alfa for the treatment of anemia associated with chemotherapy in cancer patients (6, 7). Genesis Pharma holds certain exclusive rights to distribute, market and sell darbepoetin alfa in Greece and Cyprus (8). Licensee Kirin Brewery is also conducting clinical trials in Japan with the aim of obtaining approval in 2004 (9).

Darbepoetin alfa has been studied in 1598 adults with chronic renal failure for a total of 942 patient-years in 12 clinical trials at sites around the world, as reflected in the BLA submitted to the FDA. Clinical studies demonstrated that patients receiving darbepoetin alfa consistently reached target hemoglobin levels and that the treatment was generally well tolerated. The most frequent side effects in the trials were infection, hypertension, hypotension, myalgia, headache and diarrhea, some of which, however, are commonly associated with chronic renal

failure or dialysis and may not be due to darbepoetin alfa. Darbepoetin alfa acts by stimulating the bone marrow to increase the production of red blood cells (RBC) (10).

During the fourth quarter of 2000, data from the darbepoetin alfa oncology program were presented at the annual meeting of the American Society of Hematology. In a double-blind, placebo-controlled, dose-ranging phase I/II study in 163 patients, a dose-response was seen for 4 different doses of darbepoetin alfa, as evidenced by increases in hemoglobin and a decrease in transfusions. Darbepoetin alfa appeared to increase hemoglobin more quickly and to a higher level than placebo. In a second open-label, dose-escalation study, darbepoetin alfa, given weekly at 5 different dose levels was compared with 3-times-weekly injections of rHuEPO in 177 patients. A dose-dependent relationship was seen between darbepoetin alfa and both the increase in hemoglobin and the reduced need for RBC transfusions (11).

Darbepoetin alfa proved effective, alone or in combination with other therapies such as pegylated soluble tumor necrosis factor receptor type 1 (PEG-sTNF-R1) and AMG-719 in rat models of anemia of chronic inflammatory disease, increasing RBC production, RBC hemoglobinization and serum iron concentrations and decreasing siderosis (12-15).

A pharmacokinetic study of different dosing regimens (4.5, 6.75, 9 and 13.5 μg/kg) of darbepoetin alfa given once every 3 weeks in patients receiving cyclic chemotherapy for nonmyeloid malignancies supported earlier research indicating that the pharmacokinetics of the drug in these patients are predictable, linear to dose and time-dependent (16). The pharmacokinetics of darbepoetin alfa (2.25 μg/kg/week) were evaluated in anemic cancer patients receiving multiple cycles of chemotherapy. Darbepoetin alfa was begun on day 1 of chemotherapy for 3 cycles at 3-week intervals. Similar pharmacokinetic data were obtained after a single dose in cycle 1 and in cycle 3. Data on hemoglobin response indicated that darbepoetin alfa could be administered less frequently than recombinant human erythropoietin in these patients (17).

Four independent trials conducted in a total of 810 patients with nonmyeloid malignancies either receiving or not receiving chemotherapy, examined the pharmacokinetics of darbepoetin alfa. The agent was well tolerated, with no accumulation observed after multiple dosing. Treatment increased hemoglobin levels and reduced the number of RBC transfusions required during treatment. However, chemotherapy appeared to affect distribution, metabolism and/or elimination of the agent or endogenous erythropoietin, possibly mediated via myelosuppression (18).

A study conducted in 29 patients with nonmyeloid malignancies receiving multiple cycles of chemotherapy examined the pharmacokinetics of darbepoetin alfa (2.25 μg/kg/week s.c.) administered at 3-week intervals. The results obtained support a regimen of weekly or less frequent dosing for the agent. Darbepoetin alfa was well tolerated and no accumulation was observed (C_{max} = 10.6 ng/ml and 11.3 ng/ml after single and multiple doses, respectively). Trough concentrations of the agent within each chemotherapy cycle reached a maximum during the second week, after which they decreased during weeks 3 and 4. These results suggest that cytotoxic chemotherapy affects the distribution, metabolism and/or elimination of the agent (19).

In a multicenter, randomized, open-label study, 166 patients with chronic renal insufficiency and anemia were administered darbepoetin alfa 0.45 μg/kg once weekly or rHuEPO 50 U/kg twice weekly. Treatments were administered subcutaneously for up to 24 weeks. At a reduced dosing frequency (relative to rHuEPO), darbepoetin alfa was effective in correcting and maintaining hemoglobin concentrations (20).The results of this study and several of the following studies are summarized in Table IV.

A randomized phase I/II dose-escalation study examined the administration of darbepoetin alfa in anemic cancer patients receiving chemotherapy. In the first part of the study, patients were given either rHuEPO 50 IU/kg 3 times weekly or darbepoetin alfa in sequential doses of 0.5, 1, 1.5, 2.25, 4.5, 6 and 8 μg/kg/week. Doses in the second part of the study were rHuEPO 40,000 U/week or darbepoetin alfa 3, 5, 7 and 9 μg/kg every 2 weeks. Results thus far indicate that darbepoetin alfa is well tolerated and clinically effective when administered both weekly and every 2 weeks (21).

Investigators analyzed data from 2 dose-finding studies of darbepoetin alfa in anemic patients with either solid tumors or lymphoproliferative malignancies receiving chemotherapy. Subcutaneous administration of the drug for up to 12 weeks resulted in the same dose-response relationship in both patient groups (22).

A 2-part randomized study in a total of 464 anemic patients with solid tumors who were receiving multicycle chemotherapy compared the safety and efficacy of darbepoetin alfa (1.5, 2.25, 4.5 mcg/kg every week or 3, 5, 9 mcg/kg every 2 weeks) with rHuEPO (150 U 3 times/week or 40,000 U/week) as a treatment for anemia. Both agents were well tolerated, with similar safety profiles. Darbepoetin alfa given every 2 weeks was as effective in alleviating anemia as weekly dosing, suggesting that the agent can be administered less frequently. The higher doses of darbepoetin alfa appeared to result in higher hemopoietic response rates, faster response times and greater changes in baseline hemoglobin, and patients receiving higher doses required less RBC transfusions during treatment (23).

Darbepoetin alfa was administered subcutaneously once every other week in a study in anemic patients with chronic renal insufficiency. The drug was started at 0.75 μg/kg rounded to the closest fixed dose (10, 15, 20, 30, 40, 50, 60, 80, 100, 130 and 150 mg). Treatment of the first 23 enrolled patients for a minimum of 10 weeks indicated that this regimen was effective for anemia in these patients (24).

Table IV: Clinical studies of darbepoetin alfa.

Indication	Design	Treatments	n	Conclusions	Ref.
Chronic renal failure anemia	Randomized, multicenter, open	Darbepoetin, 0.45 μg/kg sc 1x/wk x 24 wk Epoetin, 50 U/kg sc 2x/wk x 23 wk	166	Darbepoetin was safe and effective in improving hemoglobin levels in patients with chronic renal failure	20
Anemia	Randomized, dose-finding, multicenter	StudyI: (n = 239) Darbepoetin, 0.5 μg/kg/wk Darbepoetin, 1.0 μg/kg/wk Darbepoetin, 1.5 μg/kg/wk Darbepoetin, 2.25 μg/kg/wk Darbepoetin, 4.5 μg/kg/wk Darbepoetin, 6.0 μg/kg/wk Darbepoetin, 8.0 μg/kg/wk Epoetin, 150 IU/kg 3x/wk (doubled @ 8 wk if hemoglobin < 1 g/dl) Study II: (n = 176) Darbepoetin, 3.0 μg/kg 1x/2 wk Darbepoetin, 5.0 μg/kg 1x/2 wk Darbepoetin, 7.0 μg/kg 1x/2 wk Darbepoetin, 9.0 μg/kg 1x/2 wk Epoetin, 4000 U/wk (increased to 60.000 U/wk @ 6 wk if hemoglobin < 1 g/dl)	415	Darbepoetin was effective and well tolerated administered either weekly or every other week	21
Anemia	Dose-finding	Darbepoetin, 1.0 μg/kg sc 1x/wk x 12 wk Darbepoetin, 2.25 μg/kg sc 1x/wk x 12 wk Darbepoetin, 4.5 μg/kg sc 1x/wk x 12 wk	183	Darbepoetin was safe and effective in reversing chemotherapy-induced anemia	22
Anemia	Randomized, dose-finding, multicenter	Study I: (n = 288) Darbepoetin, 1.5 μg/kg/wk Darbepoetin, 2.25 μg/kg/wk Darbepoetin, 4.5 μg/kg/wk Darbepoetin, 3.0 μg/kg x 1x/2 wk Epoetin, 150 IU/kg 3x/wk Study II: (n = 176) Darbepoetin, 5.0 μg/kg 1x/2 wk Darbepoetin, 9.0 μg/kg 1x/2 wk Epoetin, 4000 U/wk	464	Darbepoetin was effective and well tolerated administered either weekly or every other wekk	23
Chronic renal failure anemia		Darbepoetin, 0.75 μg/kg (rounded to the nearest fixed dose: 10, 15, 20, 30, 40, 50, 60, 80, 100, 130 and 150 μg) x 10 wk	23	Darbepoetin was safe and effective for the treatment of anemia in chronic renal failure patients	24
Anemia	Open, dose-finding	Darbepoetin, 0.5 μg/kg 1x/wk x 12 wk Darbepoetin, 1.0 μg/kg 1x/wk x 12 wk Darbepoetin, 2.25 μg/kg 1x/wk x 12 wk Darbepoetin, 4.5 μg/kg 1x/wk x 12 wk	99	Darbepoetin was well tolerated and effective in a dose-related manner in increasing hemoglobin llevels in anemia associated with malignancies	25
Anemia	Randomized, double-blind, dose-finding, multicenter	Darbepoetin, 1.0 μg/kg sc 1x/wk x 12 wk Darbepoetin, 2.25 μg/kg sc 1x/wk x 12 wk Darbepoetin, 4.5 μg/kg sc 1x/wk x 12 wk Placebo	66	Darbepoetin was effective in increasing hemoglobin levels and reducing red blood cells transfusions in patients with anemia associated with lymphoproliferative malignancies	26
Anemia	Open, dose-finding, multicenter	Darbepoetin, 0.5 μg/kg sc 1x/wk x 12 wk (n= 13) Darbepoetin, 1.5 μg/kg sc 1x/wk x 12 wk (n = 35) Darbepoetin, 2.25 μg/kg sc 1x/wk x 12 wk (n = 59)	107	Results suggested a dose-response relationship in the proportion of patients responding and mean change in hemoglobin	27
Anemia	Open dose-finding, multicenter	Darbepoetin, 0.5 μg/kg sc 1x/wk x 12 wk (n = 6) Darbepoetin, 1 μg/kg sc 1x/wk x 12 wk (n = 33) Darbepoetin, 2.25 μg/kg sc 1x/wk x 12 wk (n = 28) Darbepoetin, 4.5 μg/kg sc 1x/wk x 12 wk (n = 30)	87	A dose-response in terms of increase in hemoglobin levels and percent recovery was observed	28

Darbepoetin alfa treatment at doses of 0.5, 1, 2.25 or 4.5 μg/kg/week was assessed in anemic patients with nonmyeloid malignancies not receiving chemotherapy. Treatment lasted for as long as 12 weeks. Dose-related increases in change in hemoglobin, patients achieving a hemoglobin response and patients achieving a hemoglobin correction were observed. The treatment was well tolerated and without dose-limiting toxicities (25).

A randomized, placebo-controlled phase II trial evaluated s.c. darbepoetin alfa 1, 2.25 and 4.5 μg/kg or placebo in 66 anemic patients with lymphoproliferative malignancies who were receiving chemotherapy. Darbepoetin alfa was administered once a week for up to 12 weeks. Darbepoetin alfa treatment increased the number of patients achieving a hemoglobin response and reduced the number of patients undergoing RBC transfusions (26).

The safety and efficacy of darbepoetin alfa (0.5, 1.5 or 2.25 μg/kg/week for up to 12 weeks) as a treatment for anemia were examined in an ongoing multicenter phase I/II dose-escalation study involving 107 anemic patients with solid tumors receiving multicycle chemotherapy. The agent appeared to be well tolerated with adverse events consistent with cytotoxic chemotherapy seen in all treatment groups. No antibody formation was observed throughout the 12-week treatment period and 4-week follow-up. The mean changes in hemoglobin observed in treated patients at week 4 and after 12 weeks were dose-dependent (1.24, 1.73 and 2.15 g/dl, respectively) (27).

The safety and efficacy of darbepoetin alfa (0.5, 1, 2.25 or 4.5 μg/kg/week for up to 12 weeks) as a treatment for anemia were examined in an open-label dose-finding study in 89 anemic patients with nonmyeloid malignancies who were not receiving chemotherapy. The treatment was well tolerated and no dose-limiting toxicities or severe treatment-related adverse events were observed. The efficacy of the agent in increasing hemoglobin was dose-dependent. Of the patients receiving 1, 2.25 and 4.45 μg/kg darbepoetin alfa, 61, 67 and 83%, respectively, responded to treatment (28).

Methods for the production of hyperglycosylated erythropoietin analogs, particularly darbepoetin alfa, and compositions containing them for the prevention and treatment of anemia have been claimed (29).

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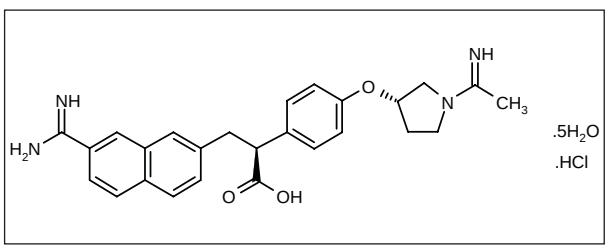
DX-9065a



DX-9065a is a synthetic, low-molecular-weight, nonpeptide compound from Daiichi Pharmaceutical which selectively and reversibly inhibits factor Xa.

In human peripheral mononuclear cells, DX-9065a suppressed activated factor X-induced tissue factor expression. In rats with lipopolysaccharide-induced endotoxemia, the drug reduced tissue factor and tissue factor mRNA expression levels in the liver (1).

In vitro, DX-9065a decreased the total activity of formed thrombin but had little effect on thrombin formation time, while the direct thrombin inhibitor argatroban inhibited thrombin activity to the same degree and prolonged the time taken to reach maximal thrombin activity (2).

The antithrombotic and antiproliferative effects of DX-9065a have been examined and compared to those of the indirect factor Xa inhibitor synthetic heparin pentasaccharide. Both pentasaccharide (250 U/kg by i.v. bolus) and DX-9065a (1 mg/kg by i.v. bolus) prevented venous thrombus formation in a rabbit model of jugular vein thrombosis induced by balloon catheter injury to the vessel wall and partial stasis. These compounds also prevented thrombotic reocclusion after successful thrombolysis with rtPA (recombinant tissue-type plasminogen activator) in this model, and significantly shortened the time to lysis with rtPA. In a rat model of vascular smooth muscle cell (VSMC) proliferation following mechanical injury to the carotid artery wall, pentasaccharide (1000 and 2000 U/kg s.c.) and DX-9065a (2.5, 5 and 10 mg/kg s.c.), given prior to vessel wall damage, were associated with a significant decrease in VSMC proliferation. Altogether, these results suggest that direct and indirect factor Xa inhibitors act as potent antithrombotic agents, enhance the activity of thrombolytics and exert antiproliferative effects which may be useful for preventing restenosis (3).

In a double-blind, placebo-controlled study in 35 healthy volunteers administered s.c. DX-9065a (2.5, 5 or 10 mg), a good correlation was seen between dose and plasma concentrations of the drug. Peak plasma levels were reached in 1 h and decreased to below the limits of detection within 4-8 h after injection (4).

DX-9065a was compared to the low-molecular-weight heparin enoxaparin in an open-label, escalating-dose, crossover study in 6 healthy male volunteers. The subjects received DX-9065a 1 mg by i.v. bolus + 0.5 mg by infusion over 2 h, followed by an additional 1-mg bolus + 1.25 mg by infusion, followed by a final 1-mg bolus + 2.5 mg by infusion, or enoxaparin administered s.c. at 1 mg/kg. Using a perfusion chamber, alterations in platelet thrombus formation before and after drug administration were quantified at high and low shear rates. At high shear rates, platelet thrombus formation as compared to baseline was 94% for enoxaparin at 4 h after administration and 99% (1 mg + 0.5 mg), 81% (1 mg + 1.25 mg) and 67% (1 mg + 2.5 mg) for DX-9065a at 2 h following administration of each dose. At low shear rates, platelet thrombus formation as compared to baseline was 98% for enoxaparin at 4 h following administration and 98% (1 mg + 0.5 mg), 89% (1 mg + 1.25 mg) and 75% (1 mg + 2.5 mg) for DX-9065a at 2 h after administration of each dose. Moreover, unlike enoxaparin, DX-9065a did not produce a significant prolongation of aPTT or bleeding time at any of the doses tested. Therefore, the reduction in platelet thrombus formation under conditions of high and low shear rates on DX-9065a suggests that direct factor Xa inhibition may have a role in the prevention of thromboembolic episodes (5, 6) (Table V).

The double-blind, randomized, placebo-controlled phase IB XaNADU (Xa Neutralization for Atherosclerotic Disease Understanding) study examined weight-adjusted

Table V: Clinical studies of DX-9065a.

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Crossover, dose-finding, open	DX-9065a, 1 mg iv bolus → 0.5 mg iv over 2 h DX-9065a, 1 mg iv bolus → 1.25 mg iv over 2 h DX-9065a, 1 mg iv bolus → 2.5 mg iv over 2 h Enoxaparin, 1 mg/kg sc	6	DX-9065a reduced platelet thrombus formation at both high and low shear rate conditions by inhibiting factor Xa, suggesting a possible effect in the prevention of thromboembolic episodes	5, 6

72-h continuous i.v. infusions of DX-9065a targeted to achieve plasma levels of 15, 50, 100 and 200 ng/ml, in comparison to placebo, in 73 older patients with stable coronary artery disease. A close correlation between plasma levels of DX-9065a and functional anti-Xa activity was seen and pharmacokinetics and pharmacodynamics were predictable. The incidence of minor bleeding was comparable in all groups and no significant differences were seen in median hemoglobin, platelets, serum creatinine or liver function. A dose-response relationship was observed (7, 8).

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Original monograph - Drugs Fut 1995, 20(6): 564.

Lanoteplase

A genetically engineered recombinant form of the naturally occurring clot-busting protein novel plasminogen activator (nPA), lanoteplase is in phase III development at Bristol-Myers Squibb for the treatment of myocardial infarction. Recombinant nPA was discovered by Genetics Institute and licensed to Bristol-Myers Squibb for the U.S. and to Suntory for Japan.

Investigators used data from 13,253 patients with S-T segment elevation myocardial infarction (STEMI) randomized to receive lanoteplase or alteplase in the InTIME-II (Intravenous nPA for Treatment of Infarcting Myocardium Early) trial to develop a strong risk index based on age, heart rate and systolic blood pressure for use in the rapid triage of emergency care patients with STEMI (1, 2). Analysis of hospital facilities and outcome data from 15,078 patients enrolled in this trial revealed variation in the availability of on-site catheterization but no major effect on patient outcomes (3). A substudy undertaken as part of the InTIME-II trial of acute myocardial infarction in 2719 patients administered lanoteplase or alteplase determined that early and medium-term mortality can be predicted more accurately with the existing S-T segment deviation in the single electrocardiograph lead with maximum deviation 90 min after starting thrombolysis than by the sum of early resolution of S-T segment elevation (4). A risk stratification scale for intracranial hemorrhage was developed from data from the InTIME-II trial. The risk of intracranial hemorrhage in patients receiving thrombolysis was assessed with a weighted score based on prior cerebrovascular disease, age, lanoteplase treatment, weight, prior nifedipine treatment, systolic blood pressure and prior antiplatelet therapy other than aspirin (5). Examination of baseline characteristics, management and outcomes in different

Table VI: Clinical studies of lanoteplase.

Indication	Design	Treatments	n	Conclusions	Ref.
Myocardial infarction	Randomized, double-blind, multicenter	Lanoteplase, 120 kU/kg iv bolus sd + Aspirin, 100-325 mg/d + Heparin, 70 U/kg iv bolus → Heparin, 15 U/h iv infusion Alteplase, 15 mg iv bolus sd → 0.75 mg/kg iv infusion x 30 min → 0.5 mg/kg iv infusion x 60 min + Aspirin, 100-325 mg/d + Heparin, 70 U/kg iv bolus → Heparin, 15 U/h iv infusion	15,078	There was a marked variability in management by the availability of on-site catheterization with no major differences in patient outcomes. Lanoteplase *vs.* alteplase had a similar mortality rate in acute myocardial infarction	3
Myocardiañ infarction	Randomized, multicenter	Lanoteplase, 120 kU/kg iv bolus (n = 10,038) Alteplase, 100 mg iv over 90 min (n = 4990)	15,060	Lanoteplase induced a higher rate of intracranial hemorrhage than alteplase. Prior cerebrovascular disease, age > 75 years, prior antiplatelet or nifedipine therapy, weight > 67 kg and systolic blood pressure > 160 mmHg were good predictors of the risk of intracranial hemorrhage	5
Myocardial infarction	Randomized, double-blind, multicenter	Lanoteplase, 120 kU/kg iv bolus sd Alteplase, 15 mg iv bolus sd → 0.75 mg/kg over 30 min → 0.5 mg/kg over 60 min	15,078	Significant regional differences in mortality persisted even after adjusting for baseline patient characteristics and consideration of differences in hospital features, which are not explained by the variation in the use of revascularization. These variations were not observed when comparing two countries in each of two regions, despite differences in the use of cardiac procedures	6
Myocardial infarction	Randomized, multicenter	Study I: TIMI 14 (n = 544) Reteplase Alteplase Abciximab Study II: InTIME II (n = 763) Lanoteplase Alteplase	1307	Lanoteplase, alteplase and reteplase had higher ST-segment resolution if administered early, administered in combination with abciximab and in patients with non-anterior infarcts	8
Myocardial infarction		Tenecteplase, 30-40 mg iv bolus (n = 19) Lanoteplase, 120 kU/kg iv bolus (n = 23)	42	Tenecteplase achieved more intensive fibrinolytic activity immediately after the bolus with more rapid reperfusion rate, whereas lanoteplase induced a prolonged intense activity that could explain the increased rate of intracranial hemorrhage observed in the InTIME-II study	10

geographic regions wth centers participating in the InTIME-II trial comparing alteplase and lanoteplase in myocardial infarction revealed significant variation in practice and adjusted mortality after fibrinolysis (6) (Table VI).

A review of recent, randomized controlled trials with fibrinolytic agents found that lower doses of i.v. heparin were associated with lower rates of intracranial hemorrhage. A similar pattern was found in recent trials with lanoteplase (7).

Researchers analyzed data from 544 patients randomized to combinations of reteplase, alteplase and abciximab in the TIMI 14 trial and data from 763 patients randomized to lanoteplase or alteplase in the InTIME-II trial to determine the relationship between the time to pharmacological reperfusion and S-T segment resolution. The chief factors affecting S-T segment resolution were abciximab and infarct location, although the time to reperfusion was inversely related to the probability of achieving complete resolution at 90 min (8) (Table VI).

Data from 38 studies evaluating the bolus fibrinolytic agents reteplase, lanoteplase and tenectoplase were analyzed. The efficacy and safety of tenecteplase and reteplase were similar to accelerated-infusion recombinant tissue-type plasminogen activator (tPA), although they are more convenient. Lanoteplase and heparin bolus plus infusion produced mortality rates comparable to those associated with accelerated-infusion recombinant tPA but were associated with a higher rate of intracranial hemorrhage (9).

The fibrinolytic activities of tenecteplase 30-40 mg and lanoteplase 120 kU/kg were compared in blood samples from 42 patients with acute myocardial infarction. More intense fibrinolytic activity was observed immediately after administration of tenecteplase, indicating a

more rapid reperfusion rate. Lanoteplase demonstrated intense activity 180 min after administration, possibly accounting for the increased incidence of intracranial hemorrhage in the InTIME-II trial (10) (Table VI).

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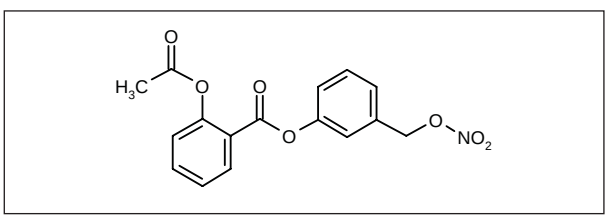
Original monograph - Drugs Fut 2002, 27(1): 21.

NCX-4016

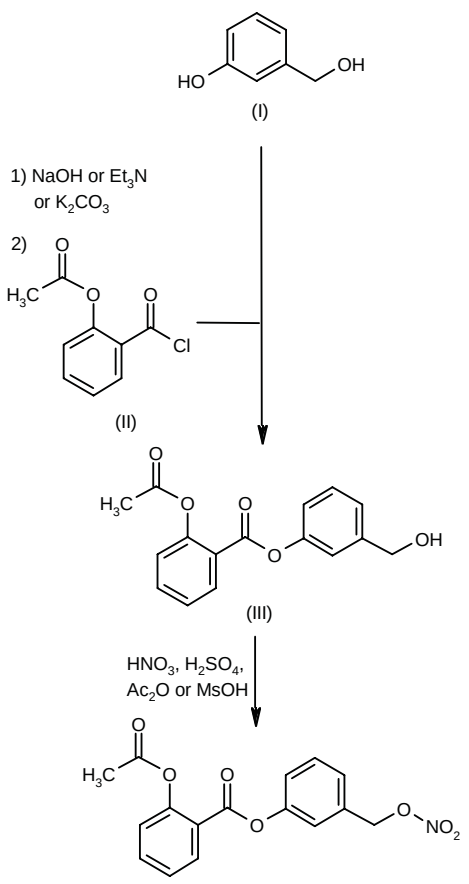


NicOx's NCX-4016, a nitric oxide (NO)-releasing aspirin derivative, is in phase I trials for the treatment of thrombosis (1).

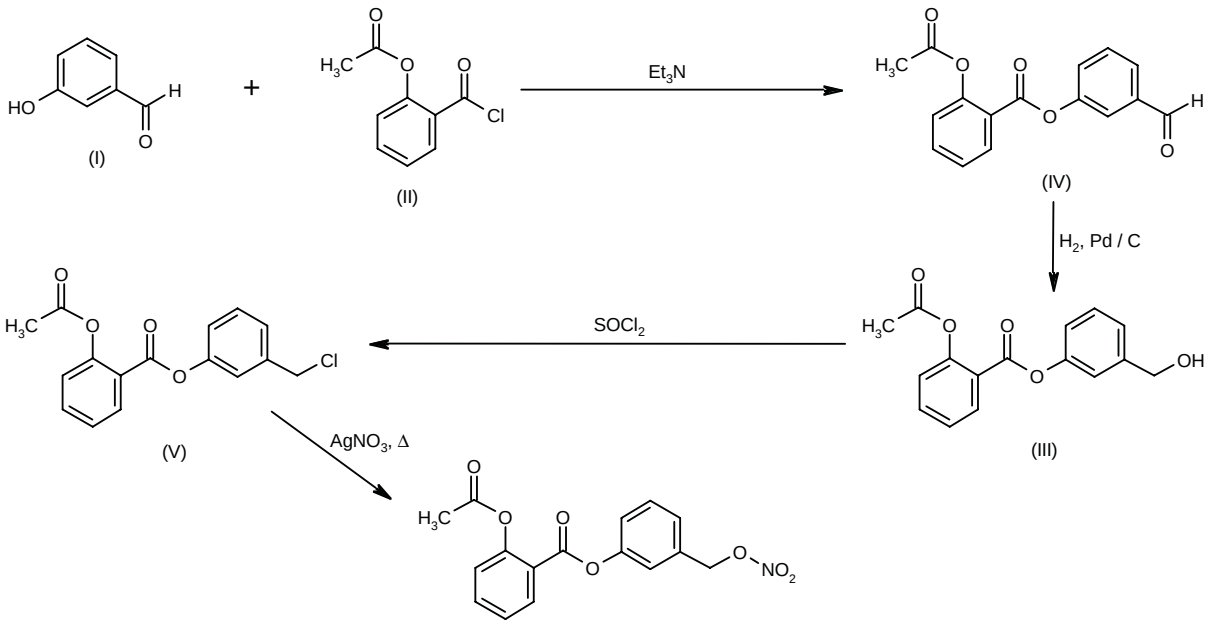
Two new methods of synthesis of NCX-4016 have been reported: Basic treatment of 3-hydroxybenzyl alcohol (I) with either NaOH in dichloromethane, Et_3N in toluene or K_2CO_3 in acetone, followed by reaction with acetylsalicyloyl chloride (II) in the respective solvents, gives 2-acetoxybenzoic acid 3-(hydroxymethyl)phenyl ester (III). NCX-4016 is obtained by nitration of compound (III) with steaming nitric acid in dichloromethane in the presence of either sulfuric acid, acetic anhydride or methanesulfonic acid (2). Scheme 1.

Alternatively, coupling of 3-hydroxybenzaldehyde (I) with acetylsalicyloyl chloride (II) by means of Et_3N in dichloromethane affords 2-acetoxybenzoic acid 3-formylphenyl ester (IV), which is then reduced by hydrogenation over Pd/C in ethyl acetate to provide alcohol (III). Chlorination of alcohol (III) by treatment with thionyl chloride in DMF gives the chloromethyl derivative (V), which is finally converted to NCX-4016 by treatment with $AgNO_3$ in refluxing acetonitrile (3). Scheme 2.

Scheme 1: Synthesis of NCX-4016



Scheme 2: Synthesis of NCX-4016



A study in LDL cholesterol receptor-deficient mice investigated the preventive and therapeutic effects of NCX-4016 on restenosis after balloon angioplasty. NCX-4016 significantly reduced VSMC proliferation and macrophage deposition at the site of injury. By comparison, aspirin produced a more modest reduction in VSMC proliferation and did not significantly inhibit macrophage deposition. Both NCX-4016 and aspirin significantly reduced the neointimal global area as compared to controls, but mice treated with NCX-4016 showed less neointimal hyperplasia and cell density as compared to those receiving aspirin. When administered 7 days prior to and 21 days after balloon injury, NCX-4016 showed greater beneficial effects than when administered only after injury. Overall, NCX-4016 at the lowest dose tested (10 mg/kg) reduced all parameters related to restenosis as compared to both controls and aspirin at the highest dose tested (54 mg/kg). NCX-4016 may therefore have potential for reducing restenosis in individuals with concomitant hypercholesterolemia and/or gastrointestinal damage (4).

NCX-4016 exerts antithrombotic activity and cardioprotective effects in rabbits. Its cardioprotective effects have now been evaluated in anesthetized rats subjected to myocardial ischemia (30 min) and reperfusion (120 min) and compared to those of aspirin. Both drugs were administered orally for 5 days, NCX-4016 at doses of 10, 30 or 100 mg/kg and aspirin at a dose of 54 mg/kg. NCX-4016 produced marked and dose-dependent cardioprotection, evidenced by increased survival and reductions in the number of ventricular premature beats, the incidence of ventricular tachycardia and fibrillation, and infarct size, whereas aspirin was significantly less effective. For example, the highest dose of NCX-4016 completely prevented mortality, reduced the incidence of ventricular tachycardia from 100% to 36% and ventricular fibrillation from 59% to 14%, respectively, during ischemia in vehicle-treated animals, reduced the number of ventricular premature beats by 72% and reduced infarct size from 60.1% of area at risk to 22.7%. Plasma creatine phosphokinase and cardiac myeloperoxidase activities were also significantly reduced on NCX-4016 compared to both vehicle and aspirin. The addition of NCX-4016 (100 mg/kg p.o.) was associated with a marked attenuation of the aggravation of myocardial damage induced by L-NAME, confirming that the beneficial effects of the nitroderivative are due mainly to the NO moiety (5).

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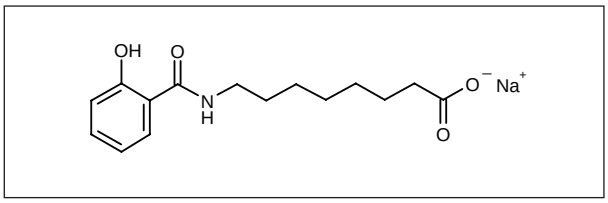
Original monograph - Drugs Fut 1997, 22(11): 1231.

Oral Heparin/SNAC



Emisphere Technologies is developing an oral formulations of heparin using the Complexing Agent Delivery System (CADDSYS) carrier SNAC. SNAC/heparin is currently in phase III trials as an oral solution for the prevention of deep vein thrombosis (DVT).

Phase I evaluation of solid oral formulations of heparin utilizing the delivery agent SNAD, structurally similar to SNAC but significantly more potent on a carrier-to-drug basis, are under way. Currently, heparin therapy is limited to injection for the treatment of DVT and for the prevention of blood clots due to postsurgical complications. An oral formulation of heparin would extend its usage for DVT prevention from the current 1- to 2-week administration in a home setting to 30 days (1, 2).

An *in vivo* study using New Zealand white rabbits subjected to iliac artery balloon dilatation examined the efficacy of i.v. (0.3 mg/kg/h) and oral (90 or 180 mg/kg b.i.d. or 120 mg/kg t.i.d.) heparin in the prevention of neointimal hyperplasia. Both i.v. and oral administration significantly inhibited neointimal hyperplasia as compared to controls. However, only i.v. heparin and the 120 mg/kg t.i.d. oral dose of heparin significantly inhibited neointimal growth after stent implantation. Thus, oral heparin may be effective against restenosis following percutaneous intervention (3).

The potential for a pharmacokinetic interaction between cimetidine or Maalox® and oral heparin and its delivery agent SNAC was examined in 2 trials in 18 healthy volunteers each. In one study, subjects received either 2.25 g SNAC/90,000 USP heparin units (18 ml) or cimetidine 300 mg given 1 h before SNAC/heparin. In the other study, subjects were given the same doses of SNAC/heparin or a 20-ml suspension of Maalox® 30 min before SNAC/heparin. Measurement of pharmacokinetic and pharmacodynamic parameters suggested that those of SNAC/heparin were not altered by single oral doses of either antacid (4) (Table VII).

Emisphere Technologies has completed the enrollment of 2292 patients at over 120 worldwide sites for the PROTECT trial, a pivotal phase III study of its oral heparin solution in the prevention of DVT following total hip replacement surgery. Among the 90% of patients who have completed the treatment phase, no significant adverse effects were attributed to the SNAC delivery agent, and less than 1% were attributed to oral heparin or subcutaneous administration of enoxaparin. The purpose of the PROTECT trial is to demonstrate the safety and efficacy of oral heparin in a 30-day treatment regimen as compared to injectable enoxaparin in a 10-day treatment regimen. Full data are expected by mid-2002. Emisphere will also conduct a second phase III study using two doses studied in the first trial to further evaluate the safety and efficacy of the product. Once the data analysis from the first trial has been completed, one of the two oral dosing arms in the second trial will be dropped (5).

Liquid heparin formulations comprising aqueous compositions containing SNAC, heparin and a polysaccharide as sucrose have been claimed (6).

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Table VII: Clinical study of oral heparin.

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized	Study I: SNAC/USP Heparin, 2.25 g/90,000 U po sd (n = 9) SNAC/USP Heparin, 2.25 g/90,000 U po sd + Cimetidine, 300 mg po sd (1 h before heparin) (n = 9) Study II: SNAC/USP Heparin, 2.25 g/90,000 U po sd (n = 9) SNAC/USP Heparin, 2.25 g/90,000 U po sd + Maalox, 20 ml suspension po sd (30 min before heparin) (n = 9)	36	Neither cimetidine nor Maalox® interfered with the effects of heparin on factor Xa	4

4. Abbas, R., Leone-Bay, A., Osgood, G., Rivera-Schaub, T., Kisicki, C., Marder, V.J., Baughman, R.A. *Clinical pharmacokinetic and pharmacodynamic interaction studies to evaluate effects of antacid (cimetidine & Maalox) pretreatment on the absorption of heparin and its delivery agent, SNAC, following oral administration in healthy subjects*. Blood 2001, 98(11, Part 2): Abst 3975.

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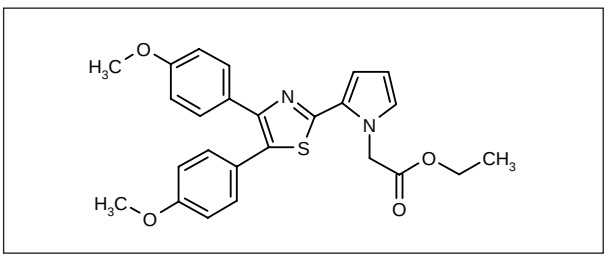
Original monograph - Drugs Fut 1997, 22(8): 885.

Pamicogrel



The antiplatelet agent pamicogrel (KBT-3022, KB-3022, TO-192) is under late-stage development by Nippon Organon and Torii.

A study involving a total of 21 elderly and nonelderly patients with chronic arterial occlusive disease (arteriosclerosis obliterans or thromboangiitis obliterans) examined the effects of pamicogrel (5 mg once daily p.o. for 6 weeks) on platelet aggregation. Examination of platelets of 8 elderly and 9 nonelderly patients showed that the agent significantly inhibited arachidonic acid-induced platelet aggregation at week 2 as compared to baseline. Platelet aggregation induced by ADP was also significantly inhibited in elderly and nonelderly patients. Furthermore, at week 6, collagen-induced platelet aggregation was significantly inhibited. Plasma clearance rates were similar in both groups and > 80% of the patients showed recovery to 80% of baseline values 7 days after the final dose, indicating that the antiplatelet effects of pamicogrel are reversible (1).

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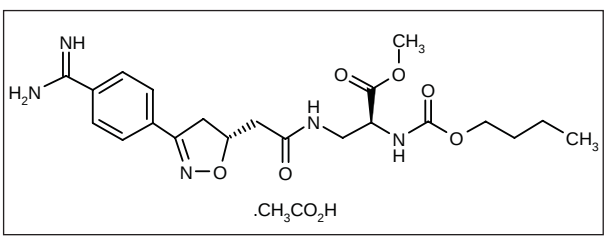
Roxifiban Acetate



An oral gpIIb/IIIa inhibitor, roxifiban acetate (Lumaxis, DMP-754; Bristol-Myers Squibb) is currently undergoing phase III trials in combination with aspirin in patients with moderate to severe peripheral arterial disease (PAD) (1).

A study that examined the platelet gpIIb/IIIa binding profiles for the active form of roxifiban (XV-459) found that the drug binds to the same binding site(s) as other RGD mimetics, as evidenced by the competitive inhibition of binding to human platelets. XV-459 competed with the FITC-labeled gpIIb/IIIa antagonist cyclic RDG peptidomimetic XL-086. XV-459 had the highest potency in inhibiting [^{3}H]-XV-459, [^{3}H]-DMP-728, [^{125}I]-echistatin and [^{125}I]-fibrinogen binding to human platelets as compared to other RGD mimetics. The α-carbon next to the carboxy terminal was found to be an exosite for binding of members of the isoxazoline roxifiban series to human platelets. Thus, roxifiban displayed a distinct binding profile as compared to other mimetics, exhibiting high-affinity binding to activated and resting platelets with a relatively slow dissociation rate (2).

A study using computerized thromboelastography examined the effects of tinzaparin, tirofiban, roxifiban, abciximab and eptifibatide on *ex vivo* tissue factor-induced platelet-fibrin clot strength. When dogs were treated with subeffective s.c. doses of roxifiban (0.1 mg/kg) and/or tinzaparin (100 IU/kg), clot strength was significantly increased by 8-fold. While treatment with abciximab and roxifiban inhibited enhancement of clot strength, eptifibatide and tirofiban were less effective. Synergistic improvements in tissue factor-mediated antiplatelet and anticoagulant effects were seen following administration of subeffective doses of tinzaparin in combination with roxifiban or abciximab. Administration of subeffective doses of tinzaparin together with clinically effective doses of tirofiban or eptifibatide caused significant synergistic inhibition of platelet-fibrin clot strength. Results indicate that low-dose tinzaparin in combination

with low-dose abciximab or roxifiban or full-dose tirofiban or eptifibatide may be effective in the prevention and treatment of thromboembolic disorders (3).

Researchers assessed the safety and efficacy of combined administration of the gpIIb/IIIa antagonist roxifiban and the low-molecular-weight heparin Innohep® (tinzaparin sodium) in a guinea pig model of arterial thrombosis and in a guinea pig cuticle bleeding model. A prolongation of the occlusion time was observed in animals receiving i.v. roxifiban (0.8 mg/kg) or Innohep® (150 IU/kg). Innohep® also caused a prolongation of clotting time, whereas roxifiban had no effect on this parameter. Innohep® led to a 30% peak inhibition of ADP-induced platelet aggregation, as compared to the 10% peak inhibition caused by roxifiban. In the thrombosis model, combined administration of roxifiban and Innohep® caused an increase in occlusion time which was greater than additive compared to the two drugs administered separately; however, in the bleeding model, combined administration of the two drugs caused an additive effect on bleeding time. These data demonstrate that the combined administration of this gpIIb/IIIa antagonist and low-molecular-weight heparin offers an improved efficacy/safety ratio as compared to the agents as used alone (4).

A sensitive, specific and cost-effective double-antibody radioimmunoassay for determining the active moiety of the oral ester prodrug roxifiban acetate in clinical studies has been developed. The method has been validated in 2 phase II clinical trials and is currently in use in the ongoing phase III trial, and has demonstrated a sensitivity and specificity comparable to the previous costly LC/MS/MS method, while being more rapid and much less expensive (5).

In *in vivo* studies and *in vitro* experiments in rat, mouse and human liver slices and dog intestinal preparations, roxifiban was found to be rapidly hydrolyzed to the zwitterion XV-459, which was further metabolized only to a small extent. Roxifiban had limited absorption following oral dosing of dogs with the radiolabeled parent compound and the majority of the radioactivity was excreted in feces. Following i.v. administration of [^{14}C]-roxifiban, radioactivity was detected in rat urine and bile and urine of dogs. XV-459 was metabolized extrahepatically by dog gut flora, resulting in an isoxazoline ring-opened metabolite, and hepatic metabolism *in vitro* resulted in hydroxylation of the isoxazoline ring. These hydroxylated metabolites were not found in urine or plasma of roxifiban-treated human subjects (6).

The comparative pharmacokinetics and pharmacodynamics of roxifiban in patients with chronic stable coronary artery disease (CAD) and healthy subjects were reported. Data from 84 patients with CAD receiving doses of roxifiban of 0.25-2.5 mg once daily for 7-30 days were compared to those from healthy male subjects receiving 0.75-1.25 mg once daily for 7 days. The results indicated no significant differences in the PK/PD profile of roxifiban between CAD patients and healthy subjects (7).

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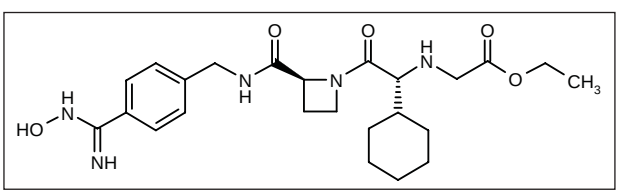
Ximelagatran



Ximelagatran (H-376/95, Exanta™; AstraZeneca), an oral direct thrombin inhibitor and the prodrug of melagatran, is in phase III trials for the treatment of deep vein blood clots, the prevention of blood clots following total hip or knee replacement surgery and for the prevention of stroke in patients with atrial fibrillation (1).

In rats administered high doses of melagatran, the addition of activated prothrombin complex concentrate significantly shortened prolonged bleeding time and reduced blood loss without potentiating thrombus formation. These effects were much weaker in rats in which recombinant factor VIIa was added to melagatran (2).

The results from a study in healthy volunteers demonstrated that the pharmacokinetics of ximelagatran and melagatran are independent of ethnic origin (3).

A study in healthy volunteers demonstrated that concomitant administration of acetylsalicylic acid and melagatran was not associated with clinically significant pharmacokinetic or pharmacodynamic interactions (4).

Table VIII: Clinical studies of ximelagatran.

Indication	Design	Treatments	n	Conclusions	Ref.
Deep vein thrombosis prophylaxis	Randomized, double-blind, multicenter	Melagatran, 3 mg sc bid sd → Ximelagatran, 24 mg po bid x 35 d (n = 30) Melagatran, 3 mg sc bid sd → Ximelagatran, 24 mg po bid x 8 d (n = 27) Dalteparin, 5000 IU sc od x 7-9 d (n = 29)	86	Ximelagatran was safe and as effective as dalteparin as a prophylactic agent for venous thromboembolism in abdominal surgery	8
Arthroplasty, deep vein thrombosis prophylaxis	Randomized, double-blind, dose-finding, multicenter	Ximelagatran, 8 mg po bid x 6-12 d (n = 85) Ximelagatran, 12 mg po bid x 6-12 d (n = 134) Ximelagatran, 18 mg po bid x 6-12 d (n = 126) Ximelagatran, 24 mg po bid x 6-12 d (n = 130) Enoxaparin, 30 mg sc bid x 6-12 d (n = 125)	594	Oral ximelagatran was safe and effective as a prophylactic agent in venous thromboembolism in knee arthroplasty	9
Deep vein thrombosis prophylaxis	Randomized, double-blind, multicenter	Ximelagatran, 24 mg po bid x 7-12 d (starting after surgery) Warfarin po od (adjusted to INR 2.5) x 7-12 d (starting before surgery)	675	Ximelagatran 24 mg p.o. was safe and effective as a prophylactic agent for venous thromboembolism in arthroplasty, and did not need routine coagulation monitoring	10
Arthroplasty	Randomized, dose-finding, multicenter	Melagatran, 1 mg sc bid (starting immediately before surgery) x 2 d → Ximelagatran, 6 mg po bid x 6-9 d (n = 34) Melagatran, 2 mg sc bid (starting immediately before surgery) x 2 d → Ximelagatran, 12 mg po bid x 6-9 d (n = 34) Melagatran, 4 mg sc bid (starting immediately before surgery) x 2 d → Ximelagatran, 24 mg po bid x 6-9 d (n = 34) Dalteparin, 500 IU sc od (starting in the evening before surgery) (n = 33)	135	Subcutaneous melagatran followed by oral ximelagatran was found to be safe, well tolerated and effective for the prevention of venous thromboembolism in patients undergoing orthopedic surgery	11

Before and after administration of s.c. ximelagatran 60 mg p.o., dalteparin 120 IU/kg or control to healthy volunteers, shed blood was analyzed for markers of thrombin generation. Thrombin generation was found to be inhibited by ximelagatran, as evidenced by significant reductions in prothrombin fragment 1+2 and thrombin-antithrombin complex, after acute activation of coagulation (5).

Different aspects of the pharmacokinetic/pharmacodynamic profile of melagatran following oral administration of the prodrug have been described. Ximelagatran is rapidly converted to the active form, which is a selective, competitive and direct thrombin inhibitor. A large, multicenter, randomized, parallel-group, dose-ranging study was conducted in patients undergoing total knee arthroplasty administered either oral ximelagatran at doses of 8, 12, 18 or 24 mg b.i.d. or s.c. enoxaparin at a dose of 30 mg b.i.d., beginning 12-24 h before surgery. Data from 455 patients showed that the pharmacokinetics of melagatran were proportional to dose. The highest dose of ximelagatran was superior to enoxaparin as regards incidence of DVT (15.8% *vs*. 22.7%) and showed comparable safety (6).

A study examined and compared the pharmacokinetics of melagatran in young and elderly healthy subjects and in patients undergoing total knee or hip replacement surgery. All healthy subjects were administered a single i.v. infusion of melagatran of 2 mg and then randomized to receive single oral doses of ximelagatran 20 mg with or without food, and the patients received s.c. melagatran or s.c. melagatran plus oral ximelagatran for 8-11 days following surgery. Pharmacokinetics of melagatran were similar in healthy subjects and patients. No effect was seen for food and the bioavailability of melagatran showed little interindividual variability. The clearance of melagatran was reduced with age and correlated with renal function and creatinine clearance (7).

In a double-blind, randomized trial in patients undergoing open abdominal and/or pelvic surgery, s.c. melagatran 3 mg b.i.d. was followed by oral ximelagatran 24 mg b.i.d. postoperatively for either 35 days or 8 days followed by placebo until postoperative day 35. A third group of patients received s.c. dalteparin 5000 IU before surgery, then once daily for 7-9 days followed by placebo until postoperative day 35. Oral ximelagatran given for 3-8 days postoperatively resulted in good bioavailability of melagatran. Both the standard and prolonged prophylaxis regimens were comparable to treatment with dalteparin (8) The results of this study and those that follow are summarized in Table VIII.

A randomized, multicenter, dose-finding trial evaluated ximelagatran and enoxaparin as prophylaxis against venous thromboembolism in 600 patients undergoing total knee replacement. Patients were administered ximelagatran (8, 12, 18 or 24 mg p.o. b.i.d.) or enoxaparin (30 mg s.c. b.i.d.) 12-24 h after surgery and continued for 6-12 days. The rates of overall venous thromboembolism did not differ significantly between enoxaparin and the 24-mg dose of ximelagatran (9).

A multicenter, randomized, double-blind trial in 680 patients undergoing total knee arthroplasty compared the incidence of venous thromboembolism (VTE) with oral ximelagatran 24 mg b.i.d. given the morning after surgery and oral warfarin given the evening of the day of surgery. Treatment with ximelagatran was found to be as effective as warfarin in preventing VTE. Ximelagatran was safe and routine coagulation monitoring and dose adjustments were not necessary (10).

A total of 136 patients undergoing total hip or total knee replacement and enrolled in a randomized study received either s.c. melagatran (1, 2 or 4 mg b.i.d.) for 2 days beginning just before surgery and followed by oral ximelagatran (6, 12 or 24 mg b.i.d.) for 6-9 days, or once-daily dalteparin (5000 IU s.c.) begun the evening before surgery and continued for 8-11 days. Ximelagatran and melagatran demonstrated potential in this setting, with the incidence of deep vein thrombosis comparable between treatment groups and total bleeding on melagatran/ximelagatran similar to that in the dalteparin group (11).

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