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Annual Update 2003: Drugs for Hematological Disorders

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Abstract

This month's Annual Update 2003 is dedicated to the treatment of hematological disorders and is comprised of a Compendium of 89 drugs and other products that are in active clinical development for the treatment of hematological disorders or which have been launched for the first time since 2002. The Compendium also includes products that had previously been marketed for another indication and are now being studied or have been introduced for a hematological indication. Products featured in the monograph updates section include clopidogrel hydrogensulfate, CS-747, darbepoetin alfa, decitabine, DX-9065a, fondaparinux sodium, idraparinux sodium, oral heparin/SNAC and ximelagatran/melagatran.

Introduction

This month's Annual Update 2003 is dedicated to the treatment of hematological disorders and is comprised of a Compendium of 89 drugs and other products that are in active clinical development for the treatment of hematological disorders or which have been launched for the first time since 2002. The Compendium also includes products that had previously been marketed for another indication and are now being studied or have been introduced for a hematological indication. Products featured in the monograph updates section include clopidogrel hydrogensulfate, CS-747, darbepoetin alfa, decitabine, DX-9065a, fondaparinux sodium, idraparinux sodium, oral heparin/SNAC and ximelagatran/melagatran.

Annual Update 2003: Drugs for Hematological Disorders

Drug	Source	Condition	Phase
AAV-FIX	Avigen	Hemophilia B	I/II
Activated Protein C Concentrate	Teijin	Embolism, pulmonary	L-2001
	Teijin	Thrombosis, deep venous	L-2001
	Teijin	Disseminated intravascular coagulation	Prereg.
AJW-200	Ajinomoto	Thrombosis	I
Alfimeprase	Nuvelo	Occlusion, peripheral arterial and catheter	II
Amediplase[2]	Menarini	Myocardial infarction	III
AR-C126532	AstraZeneca	Thrombosis, arterial	I
BB-10153	British Biotech	Myocardial infarction	II
BGC-728	BTG	Stroke	I
	BTG	Myocardial infarction	I
Bivalirudin[1]	The Medicines Co.	Acute coronary syndrome	II
	The Medicines Co.	Occlusion, arterial coronary	III
Cilostazol[1]	Otsuka	Stroke	Prereg.
Clopidogrel Hydrogensulfate[1,2]	Sanofi-Synthélabo/Bristol-Myers Squibb	Acute coronary syndrome	R-2002
CS-747	Lilly/Sankyo/Ube	Stroke	II
	Lilly/Sankyo/Ube	Acute coronary syndrome	II
D-003	Cent. Nac. Invest. Cientificas/Lab. Dalmer	Thrombosis	I
Dabigatran Etexilate	Boehringer Ingelheim	Thrombosis, deep venous	II
Daclizumab[1]	National Institutes of Health	Purpura, thrombocytopenic	II
Darbepoetin Alfa[2]	Amgen/Kirin Brewery	Anemia, chemotherapy-induced	L-2002
	Amgen/Kirin Brewery	Anemia, renal failure	L-2001
Decitabine[2]	SuperGen	Anemia, sickle cell	II
Desmoteplase	PAION	Stroke, ischemic	II
DPC-906	Bristol-Myers Squibb	Thrombosis, deep venous	II
DX-9065a[2]	Daiichi Pharmaceutical	Thrombosis	II
Eculizumab	Alexion Pharmaceuticals	Hemoglobinuria	I
Epoetin Beta[1]	Roche	Anemia in radiotherapy	III
Epoetin Delta	Aventis Pharma/Transkaryotic Therapies	Anemia	III
	Aventis Pharma/Transkaryotic Therapies	Anemia, renal failure	R-2002
Eptacog Alfa[1]	Novo Nordisk	Hemorrhage	II
Eptifibatide[1,2]	Millennium/Schering-Plough	CABG surgery	II
	Millennium/Schering-Plough	Myocardial infarction	III
F(ab')2 FRaMon	Cleveland Clinic Foundation	Thrombosis	II
Ferumoxytol	Advanced Magnetics	Anemia	II
Fondaparinux Sodium[2]	Sanofi-Synthélabo/Organon	Thrombosis prophylaxis, deep venous	L-2002
Gantofiban	Yamanouchi	Thrombosis	II
Garnocestim	GlaxoSmithKline	Cytopenias	I
GH-9001	GlycoDesign/Leo	Embolism, pulmonary	I
	GlycoDesign/Leo	Thrombosis, deep venous	I
GW-473178	GlaxoSmithKline	Thrombosis	I
HE-2200	Hollis-Eden	Neutropenia	I/II
Hemoglobin Glutamer-250	Biopure	Anemia	L-2002
Hemoglobin Raffimer	Hemosol	Surgery, arterial coronary	Prereg.
	Hemosol	Anemia, secondary	II
Hemospan	Sangart	Surgery	I
Human Protein C Concentrate	Baxter	Thrombosis	L- 2001
ICA-17043	ICAgen	Anemia, sickle cell	II
Idraparinux Sodium[2]	Organon/Sanofi-Synthélabo	Embolism, pulmonary	III
	Organon/Sanofi-Synthélabo	Thrombosis, deep venous	III
	Organon/Sanofi-Synthélabo	Stroke prevention	III
IGIV-C	Bayer	Purpura, thrombocytopenic	R-2003
JTV-803	Japan Tobacco	Thrombosis	II
KFA-1982	Kissei	Thrombosis, deep venous	I
KRN-9000[2]	Kirin Brewery/Amgen	Thrombocytopenia	I/II
MCC-977	Mitsubishi Pharma	Thrombosis, deep venous	II
Melagatran[2]	AstraZeneca	Embolism, venous	Prereg.
Microplasmin	ThromboGenics	Occlusion, peripheral arterial	I
	ThromboGenics	Stroke	I
MLN-1021	Millennium	Thrombosis, venous	I
Monteplase[1]	Eisai	Embolism, pulmonary	Prereg.
Nematode Anticoagulant Protein c2	Corvas	Acute coronary syndrome	II

Continuation

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Drug	Source	Condition	Phase
NIX-0699	Xechem	Anemia, sickle cell	L-2003
NM-702	Taisho/Nissan Chemical	Vascular disease, peripheral obstructive	II
OBI-1	Ipsen	Hemophilia	I
Oral Heparin[2]	Emisphere	Thrombosis, deep venous	III
Oxycyte	Synthetic Blood Intl.	Surgery	IND Filed
Oxygent*	Alliance/Baxter	Surgery	III
PEG-Filgrastim	Amgen	Neutropenia	R-2002
	Amgen	Neutropenia, febrile	L-2002
PEG-Sak	ThromboGenics	Myocardial infarction	II
PentaLyte	BioTime	Blood plasma volume expander	I
PHP	Curacyte	Shock, blood substitute	III
PLD-117	Pliva	Thrombocytopenia	I
Poloxamer-188	CytRx	Anemia, sickle cell	III
PolyHeme	Northfield Laboratories	Trauma	II
Polynitroxylated Hemoglobin	SynZyme	Surgery	III
PRO-38747	Genentech	Acute coronary syndrome	IND Filed
PT-100	Point Therapeutics	Neutropenia	I/II
R-744	Chugai/Roche	Anemia, cancer-related	II
	Chugai/Roche	Anemia, renal failure	II
rAHF-PFM	Baxter	Hemophilia A	Prereg.
Recombinant Human Antithrombin III	GTC Biotherapeutics	Thrombosis	II/III
Recombinant Human Factor XIII	ZymoGenetics	Congenital FXIII deficiency	I
Recombinant Human Soluble Thrombomodulin	Asahi Kasei	Disseminated intravascular coagulation	III
	Asahi Kasei	Thrombosis, deep venous	II
RG-1046	Repligen	Purpura, thrombocytopenic	I/II
rhGM-CSF	Cangene	Neutropenia	III
Rituximab[1]	Genentech	Purpura, thrombocytopenic	II
S-18886	Servier	Thrombosis, arterial	III
SB-249417	GlaxoSmithKline	Stroke	I
SB-424323	GlaxoSmithKline	Thrombosis	II
SB-497115	GlaxoSmithKline	Thrombocytopenia	I
SL-65.0472	Sanofi-Synthélabo	Thrombosis	I
SNAD/LMWH	Emisphere	Thrombosis, deep venous	I
SR-123781A	Sanofi-Synthélabo/Organon	Thrombosis	I
STC-387	Teijin	Myocardial infarction	I/II
TA-993	Tanabe Seiyaku	Atherosclerosis obliterans	II
TC-10	Teijin	Thrombosis	I/II
TKT-Factor VIII	Transkaryotic Therapies	Hemophilia A	I
TRI-50b	Trigen	Thrombosis	II
Urokinase Alfa	Abbott Labs.	Thrombosis	III
VX-563	Vertex	Anemia, sickle cell	I
Ximelagatran[2]	AstraZeneca	Thrombosis prophylaxis, deep venous	Prereg.
	AstraZeneca	Thrombosis, venous	III
YM-337	Yamanouchi	Stroke, ischemic	II
Z-335	Zeria	Atherosclerosis obliterans	II
	Zeria	Occlusion, arterial	II

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Compendium of Drugs for Hematological Disorders

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Thrombotic complications

Thrombosis is the formation of a solid blood clot in an artery or vein. Such a clot is formed by the same reactions that also stop blood flow from a wound. The human body has a finely tuned mechanism to stop bleeding called the coagulation cascade. This mechanism is triggered when the blood comes in contact with an acutely or chronically damaged blood vessel wall, *i.e.*, in the presence of a wound or atherosclerotic lesion. If the blood clot forms in the coronary artery, the result will be a myocardial infarction. If it forms in an artery of the brain, the patient will suffer a stroke. Deep vein thrombosis (DVT) occurs when a blood clot forms in a deep vein, typically in the lower extremities. The major risk associated with DVT is development of pulmonary embolism (PE). This life-threatening complication occurs when a fragment of a blood clot breaks loose from the wall of the vein and migrates to the lungs, where it blocks a pulmonary artery or one of its branches.

Drugs generally used to treat thrombotic complications fall into three basic categories: anticoagulants, which do not dissolve clots but weaken their stability and prevent further expansion; thrombolytics, which help to dissolve clots; and antiplatelet agents, which discourage new clots from forming.

Thrombolytics

Administered by intravenous infusion or directly into the clot via catheter, thrombolytic agents like streptokinase and tissue-type plasminogen activator (t-PA) target the fibrin mesh that binds clots together, causing it to disintegrate. Due to an elevated risk of bleeding complications, these agents are used only in hospitalized patients and their use is reserved for patients with new large clots and those who are at high risk of long-term complications due to a clotting disorder or other predisposing condition.

Eisai has submitted a supplemental NDA for Cleactor® (**monteplase** [rDNA origin]) for the treatment of acute PE to the Ministry of Health, Labour and Welfare in Japan. Cleactor®, a second-generation t-PA developed using recombinant DNA techniques, was granted orphan drug status in 1998 and is expected to be the first t-PA drug for this indication. It was launched for the lysis of coronary thrombus caused by acute myocardial infarction in 1998.

Menarini's **amediplase** is a novel thrombolytic agent obtained through recombinant DNA technology. The product is a hybrid plasminogen activator in which the kringle-2 domain of t-PA is linked to the catalytic protease domain of single-chain urokinase-type plasminogen activator (scu-PA). It has longer lasting and more potent thrombolytic activity than t-PA, high specificity for fibrin and a favorable safety profile. Amediplase is in phase III testing for the treatment of acute myocardial infarction.

British Biotech has completed phase I testing with the thrombolytic agent **BB-10153**, an engineered form of human plasminogen, and has advanced to phase II testing in the indication of acute myocardial infarction. This study is being conducted for the company by the U.S.-based Thrombolysis in Myocardial Infarction (TIMI) Study Group, and results are expected during the second half of 2003. However, given the size and cost of trials that will have to be conducted, further development of BB-10153 for the acute myocardial infarction indication will require a codevelopment partner.

Table I presents further information on these and other thrombolytic agents currently under active investigation for the prevention and treatment of thrombotic complications.

Antiplatelet therapy

Following the results of the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study, an extension in the indication for **clopidogrel hydrogensulfate** (Plavix®, Iscover®) has been obtained in the U.S. and in Europe for the treatment of patients with non-S-T segment elevation acute coronary syndrome (unstable angina or non-Q wave myocardial infarction). Clopidogrel, a

Table I: Thrombolytic agents in development for the prevention and treatment of thrombotic complications.

Drug Name	Source	Mechanism of Action/Description	Status (indication)
Monteplase*	Eisai	Tissue-type plasminogen activator	Prereg. (acute pulmonary embolism)
Amediplase	Menarini	Plasminogen activator	Phase III (acute myocardial infarction)
Urokinase alfa	Abbott	Urokinase	Phase III (catheter occlusion)
Desmoteplase	PAION GmbH	Plasminogen activator	Phase II (acute ischemic stroke)
rhATIII	GTC Biotherapeutics	Recombinant human antithrombin III	Phase II/III (control of blood clotting during CABG surgery in heparin-resistant patients)
Alfimeprase	Nuvelo	Modified form of the fibrin-degrading enzyme fibrolase	Phase II (peripheral arterial occlusion, catheter occlusion)
BB-10153	British Biotech	Engineered form of human plasminogen with antithrombotic and thrombolytic properties	Phase II (acute myocardial infarction)
PEG-Sak	ThromboGenics	Polyethylene glycol-derivatized recombinant staphylokinase variant	Phase II (acute myocardial infarction)
STC-387	Teijin	Undisclosed	Phase I/II (acute myocardial infarction)
Microplasmin	ThromboGenics	Recombinant active form of human microplasminogen	Phase I (peripheral arterial occlusion, acute stroke)

*Previously marketed for another indication

$P2Y_{12}$ (P2T) antagonist, had been marketed since 1998 for the treatment of atherosclerosis. Discovered by Sanofi-Synthélabo, clopidogrel was developed and is marketed in collaboration with Bristol-Myers Squibb.

Large heart attack or S-T segment elevation myocardial infarction (STEMI) is caused by the total occlusion of a coronary artery by a blood clot. Current management of STEMI is focused on breaking apart the mesh of fibrin that surrounds a clump of platelets occluding the vessel. Because the fibrinogen gpIIb/IIIa antagonist **eptifibatide** (Integrilin®) breaks up platelet clumps and prevents them from re-aggregating, it may play a role in the management of STEMI. Millennium initiated a phase III clinical trial studying this potential new use in the final quarter of 2002. Millennium is conducting another phase II clinical trial to determine whether eptifibatide, when administered prior to coronary artery bypass graft (CABG) surgery, could prevent the disruption of normal platelet activity and resultant bleeding and heart attack that occur with the use of bypass machines during on-pump CABG surgery. Eptifibatide has been marketed since 1998 by Millennium and Schering-Plough for the prevention of myocardial infarction and sudden death in patients with unstable angina and non-Q wave myocardial infarction, as well as those undergoing balloon angioplasty.

BGC-728, another fibrinogen gpIIb/IIIa antagonist, has been developed through phase I by BTG and is now being offered for licensing. This cyclic peptide compound has a rapid onset of action, is effective against all endogenous platelet activators and has demonstrated safety and tolerance in phase I clinical trials. BGC-728 is potentially applicable for the treatment and prophylaxis of acute myocardial infarction and stroke.

Further information on these and other antiplatelet therapies in active development for the prevention and treatment of thrombotic complications appears in Table II.

Anticoagulants

Anticoagulants such as warfarin and heparin prevent and treat abnormal blood clotting by decreasing levels of circulating endogenous blood clotting factors. They are effective in preventing the formation of new clots as well as preventing existing clots from becoming larger.

The synthetic specific factor Xa inhibitor **fondaparinux sodium** was introduced in the U.S. in February 2002 as Arixtra®. Codeveloped and comarketed by Organon and Sanofi-Synthélabo, fondaparinux is indicated for the prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery, hip replacement surgery or knee replacement surgery. The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of factor Xa. By selectively binding to ATIII, fondaparinux potentiates the innate neutralization of factor Xa by ATIII, thereby interrupting the blood coagulation cascade, inhibiting thrombin formation and preventing thrombus development.

Anact C for injection, a new human plasma-derived **activated protein C concentrate** from Teijin, was introduced in Japan during 2001 for the treatment of DVT and pulmonary thromboembolism due to congenital protein C deficiency. The company has filed an NDA for the supplementary indication of disseminated intravascular coagulation.

Hereditary protein C deficiency occurs in approximately 1 of every 200,000 births and often goes undiagnosed. If left untreated, the thrombotic lesions that develop can result in blindness, severe brain damage, multiorgan failure and death. Currently there is no ideal alternative to specific protein C replacement therapy. Baxter introduced its purified human plasma-derived protein C product Ceprotin (**protein C concentrate [human]**) in the E.U. in October 2001 for the treatment of purpura fulminans and coumarin-induced skin necrosis in patients with severe congenital protein C deficiency and

Table II: Antiplatelet therapies in development for the prevention and treatment of thrombotic complications.

Drug Name	Source	Mechanism of Action/Description	Status (indication)
Clopidogrel hydrogensulfate*	Sanofi-Synthélabo/Bristol-Myers Squibb	P2T antagonist	R-2002 (acute coronary syndrome)
Cilostazol*	Otsuka	PDE III inhibitor/thromboxane synthase inhibitor	Prereg. (prevention of recurrent stroke)
Eptifibatide*	Millennium/Schering-Plough	Fibrinogen gpIIb/IIIa antagonist	Phase III (myocardial infarction), Phase II (CABG surgery)
S-18886	Servier	Thromboxane A_2 receptor antagonist	Phase III (arterial thrombosis)
CS-747	Sankyo/Ube/Lilly	P2T antagonist	Phase II (secondary prevention of thrombotic complications in patients with recent ischemic stroke or acute coronary syndromes)
F(ab')2 FRaMon	Cleveland Clinic Foundation	F(ab')2 fragments of an anti-gpIIb/IIIa murine MAb	Phase II (unspecified thrombosis)
Gantofiban	Yamanouchi	Fibrinogen gpIIb/IIIa antagonist	Phase II (unspecified thrombosis)
NM-702	Taisho/Nissan Chemical	PDE3 inhibitor/PDE5 inhibitor/ thromboxane synthase inhibitor	Phase II (peripheral vascular diseases)
TA-993	Tanabe Seiyaku	1,5-Benzothiazepine derivative	Phase II (atherosclerosis obliterans)
YM-337	Yamanouchi	Humanized anti-gpIIb/IIIa MAb	Phase II (ischemic stroke)
Z-335	Zeria	Thromboxane A2 receptor antagonist	Phase II (atherosclerosis obliterans, chronic arterial occlusive disorders)
AR-C126532	AstraZeneca	P2T antagonist	Phase I (arterial thrombosis)
BGC-728	BTG	Fibrinogen gpIIb/IIIa antagonist	Phase I (prevention and treatment of myocardial infarction and stroke)
D-003	Cent. Nac. Investigaciones Científicas/Labs. Dalmer	Mixture of high aliphatic primary acids isolated and purified from sugar cane wax	Phase I (unspecified thrombosis)
SL-65.0472	Sanofi-Synthélabo	5-HT_{1B}/5-HT_{2A} antagonist	Phase I (unspecified thrombosis)

*Previously marketed for another indication

short-term prophylaxis in patients with severe congenital protein C deficiency if one or more of the following conditions are met: surgery or invasive therapy is imminent, while initiating coumarin therapy, when coumarin therapy alone is not sufficient and when coumarin therapy is not feasible. Protein C is a vitamin K-dependent anticoagulant glycoprotein synthesized in the liver and converted by the thrombin/thrombomodulin complex on the endothelial surface to activated protein C, a serine protease with potent anticoagulant and profibrinolytic effects. Administration of Ceprotin provides for an immediate, although temporary, increase in plasma levels of protein C, which is expected to control or prevent thrombotic complications in protein C-deficient patients.

Organon and codevelopment partner Sanofi-Synthélabo have initiated a pivotal phase III program for **idraparinux sodium**, a novel once-weekly anticoagulant. The trials will study the use of idraparinux for the long-term prevention of stroke in patients suffering from atrial fibrillation and the treatment of DVT and PE. These studies are designed to demonstrate that idraparinux is at least as effective and superior in safety compared to current treatments. Unlike other products, idraparinux is administered once weekly rather than daily, increasing patient convenience. In contrast to other anticoagulants, idraparinux does not require monitoring, as the phase II PERSIST trial confirmed it to be very reliable and predictable in maintaining protection against recurrent venous thromboembolism over the week.

Table III presents complete information on new anticoagulants in active development or launched in recent years for the prevention and treatment of thrombotic complications.

Neutropenia

The term neutropenia describes the situation where the number of neutrophils in the blood is too low. Neutrophils are very important in defending the body against bacterial infections, and therefore, a patient with neutropenia is more susceptible to bacterial infections. People with neutropenia get infections easily and often. Most of the infections occur in the lungs, mouth and throat, sinuses and skin. Painful mouth ulcers, gum infections, ear infections and periodontal disease are common. Severe, life-threatening infections may occur.

Neutropenia may be a primary disorder (classified as congenital, cyclic or chronic idiopathic neutropenia), or it may develop following treatment with chemotherapeutic drugs, antibiotics, antiinflammatory agents or other drugs. As many as one in three patients receiving cancer chemotherapy suffer from neutropenia. The condition has

Table III: Anticoagulants in development for the prevention and treatment of thrombotic complications.

Drug Name	Source	Mechanism of Action (route of administration)	Status (indication)
Activated protein C concentrate	Teijin	Human plasma-derived activated protein C concentrate (parenteral)	L-2001 (thrombotic disorders in patients with congenital protein C deficiency)
Protein C concentrate (human)	Baxter	Monoclonal antibody-purified, double viral-inactivated human protein C concentrate (parenteral)	L-2001 (thrombotic disorders in patients with congenital protein C deficiency)
Fondaparinux sodium	Organon/Sanofi-Synthélabo	Coagulation factor Xa inhibitor (oral)	L-2002 (prevention of DVT)
Ximelagatrin/melagatran	AstraZeneca	Thrombin inhibitor (oral/parenteral)	Prereg. (prevention of venous thromboembolism)
Bivalirudin*	The Medicines Co.	Thrombin inhibitor (parenteral)	Phase III (acute coronary syndrome, arterial coronary occlusion), Phase II (acute coronary syndrome)
Idraparinux sodium	Sanofi-Synthélabo/ Organon	Coagulation factor Xa inhibitor	Phase III (DVT, prevention of stroke)
Oral heparin	Emisphere	Heparin (capsule and tablet formulations)	Phase III (DVT)
Thrombomodulin	Asahi Kasei	Recombinant human soluble thrombomodulin (oral)	Phase III (disseminated intravascular coagulation)
Dabigatran etexilate	Boehringer Ingelheim	Thrombin inhibitor	Phase II (DVT)
DPC-906	Bristol-Myers Squibb	Coagulation factor Xa inhibitor (oral)	Phase II (DVT)
DX-9065a	Daiichi Pharmaceutical	Coagulation factor Xa inhibitor (oral)	Phase II (unspecified thrombosis)
JTV-803	Japan Tobacco	Coagulation factor Xa inhibitor (oral and parenteral)	Phase II (unspecified thrombosis)
MCC-977	Mitsubishi Pharma	Thrombin inhibitor	Phase II (DVT)
rNAPc2	Corvas	Nematode anticoagulant protein c2 (oral)	Phase II (acute coronary syndrome)
SB-424323	GlaxoSmithKline	Thrombin inhibitor	Phase II (thrombotic complications of cardiovascular disease)
TRI-50b	Trigen	Thrombin inhibitor (oral and parenteral)	Phase II (unspecified thrombosis)
TC-10	Teijin	Undisclosed	Phase I/II (unspecified thrombosis)
AJW-200	Ajinomoto	Anti-Von Willebrand factor MAb	Phase I (unspecified thrombosis)
GH-9001	Leo Denmark/ GlycoDesign (acquired by InflaZyme)	Mixture of medium-molecular-weight heparin and low-molecular-weight dermatan sulfate	Phase I (DVT, PE)
GW-473178	GlaxoSmithKline	Thrombin inhibitor	Phase I (thrombotic complications of cardiovascular disease)
KFA-1982	Kissei	Coagulation factor Xa inhibitor	Phase I (DVT)
MLN-1021	Millennium	Coagulation factor Xa inhibitor	Phase I (venous thrombosis)
Oral LMWH	Emisphere	Low-molecular-weight heparin formulated with SNAD carrier	Phase I (DVT)
SB-249417	GlaxoSmithKline	Anti-factor IXa MAb	Phase I (stroke)
SR-123781A	Sanofi-Synthébo/ Organon	Coagulation factor Xa inhibitor/thrombin inhibitor	Phase I (thromboembolic disease)
PRO-38747	Genentech	Recombinant humanized anti-tissue factor MAb fragment	IND filed (acute coronary syndrome)

*Previously marketed for another indication

also been associated with diseases such as lupus, hepatitis, rheumatoid arthritis, Sjögren's syndrome, aplastic anemia and others.

Severe neutropenia may be treated with granulocyte-colony stimulating factor (G-CSF), immunomodulators, immunoglobulins, corticosteroids, cytokines and other drugs. Bone marrow transplantation or infusion of white blood cells may be required in some patients.

Colony-stimulating factors

G-CSF stimulates the production of neutrophils and also enhances the activity of mature neutrophils, thus improving their bacteria-killing function. It acts via a receptor localized on granulocytes that binds the G-CSF to the cell and produces a signal to mature, divide or enhance function.

Amgen's **pegfilgrastim** (Neulasta™), a covalent conjugate of recombinant methionyl human granulocyte colony-stimulating factor (G-CSF, filgrastim) and monomethoxypolyethylene glycol, was first launched in the U.S. in April 2002. Pegfilgrastim is indicated for decreasing the incidence of infections, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs. Later in the year the same drug was approved in the E.U. for a similar indication: for the reduction in duration of neutropenia and the incidence of febrile neutropenia in patients treated with cytotoxic chemotherapy for malignancy, with the exception of chronic myeloid leukemia and myelodysplastic syndromes.

Hematopoietic agents

Phase I/II clinical trial results to date show that Point Therapeutics' lead product candidate **PT-100** demonstrates an improvement in severe neutropenia associated with chemotherapy and is well tolerated in patients with cancer. PT-100 is an orally active small molecule which is believed to stimulate the proliferation of hematopoietic progenitor cells and the differentiation of neutrophils. The novel activity of PT-100 is thought to be due to its ability to stimulate the production of certain cytokines and chemokines that are both hematopoietically active and known to promote the body's defense against malignant tumors.

Immunomodulators

Preclinical studies evaluating Hollis-Eden's immunomodulating compound **HE-2200** (Reversionex™) in primate models of chemotherapy-induced immune suppression have generated positive data on neutrophil recovery as well as platelet protection. HE-2200 also offers the potential advantages of significantly lower drug manufacturing costs and the potential ability to stimulate cell-mediated immunity. Based on these attributes and its study results to date, Hollis-Eden may conduct a phase II clinical trial with either HE-2200 or the related compound HE-2100 (Neumune™) in this setting.

Thrombocytopenia

Thrombocytopenia is a condition characterized by an abnormally small number of platelets in circulating blood, which may be associated with abnormal bleeding. Thrombocytopenia may be a primary (autoimmune or essential) or secondary condition, *e.g.*, as a severe complication of cancer chemotherapy.

Treatment of thrombocytopenia depends on the cause of the condition. In some cases, transfusion of platelets may be required to stop or prevent bleeding.

Thrombopoietin agonists

PLD-117, a thrombopoietin (TPO) agonist being developed by Pliva under license from Receptron, has been evaluated in phase I studies as a potential treatment for thrombocytopenia. Additional studies investigating the mechanism of action are ongoing at collaborating institutions in the U.S.

GlaxoSmithKline has commenced clinical trials with **SB-497115**, the first oral TPO growth factor to enter human development, for the treatment of thrombocytopenia. SB-497115 is a small molecule that mimics the activity of TPO, a protein that promotes the growth and production of platelets. The product is a result of a collaboration with Ligand that began in 1995. GSK has exclusive worldwide marketing rights to products resulting from the research and Ligand will receive milestone payments and royalties on sales.

KRN-9000, a recombinant version of human TPO from Kirin Brewery (codeveloped with Amgen), is in phase I/II evaluation as a promising new treatment for thrombocytopenia.

Idiopathic thrombocytopenic purpura

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune form of thrombocytopenia (see previous section) in which the body makes antibodies that target a patient's own blood platelets, resulting in premature platelet destruction and an impaired ability to form blood clots. The clinical consequences of ITP are largely dependent on platelet count and range from bruising, mucosal bleeding and nosebleeds to intracranial hemorrhage, which can be fatal. There are approximately 100,000 people in the U.S. with this condition.

Drugs that alter the immune system's attack on the platelets, such as prednisone or intravenous infusions of immune globulin, often are used, as well as surgical removal of the spleen in an attempt to increase the number of platelets and improve blood clotting. In more severe cases where these standard treatments have not shown benefit, various chemotherapy drugs such as vincristine and cyclophosphamide are used.

Immunoglobulins

In August 2002, Bayer Biological Products submitted its next-generation immune globulin intravenous (**IGIV-C**) product for regulatory approval in the U.S., Canada and Germany. Submitted under the trade name Gamunex™, the new IGIV-C product introduces a new purification process. Gamunex™ is the first newly developed IGIV product to be submitted to the FDA in over a decade. Bayer currently manufactures and distributes Gamimune® N 10%/Polyglobin® 10%, Immune Globulin Intravenous (Human) 10%, which is approved for various conditions including ITP, pediatric AIDS and bone marrow

transplant. To support the approval for Gamunex™, Bayer undertook an unprecedented licensure-relevant clinical trial program, including the largest-ever series of trials involving patients with primary immune deficiency. The clinical trial program consisted of seven trials worldwide, including more than 350 patients from leading medical centers. To establish evidence of the product's efficacy and tolerability, the trials incorporated powered, randomized, double-blind and controlled trial designs focusing on hard clinical endpoints. Of special importance were the powered and comparative (Gamunex™ *versus* Gamimune® N) trials, which are expected to demonstrate for the first time that different production methods lead to different clinical outcomes.

Immunosuppressants

Repligen has initiated a phase I/II clinical trial evaluating the activity of **RG-1046** (CTLA4-Ig) in 12 patients with refractory ITP. The product, a soluble form of a T-cell-regulatory protein that acts as a natural "off" switch, is designed to interrupt the unwanted immune response which causes the body to attack its own platelets.

Monoclonal antibodies

The monoclonal antibody **rituximab** (marketed as Rituxan®) works by binding to the CD20 antigen on the surface of normal and malignant B-cells. From there, it recruits the body's natural defenses to attack and kill the marked B-cells. Stem cells (B-cell progenitors) in bone marrow lack the CD20 antigen, allowing healthy B-cells to regenerate after treatment and return to normal levels within several months. Rituximab is in phase II testing at Genentech for the treatment of ITP. The product, which was codeveloped by Genentech and Roche under license from Idec, has been marketed for several years as an oncolytic agent.

The National Institutes of Health is sponsoring a phase II study to evaluate the activity of another monoclonal antibody, **daclizumab**, in patients with chronic ITP. Daclizumab is a humanized MAb directed to the interleukin-2 receptor that targets and impairs activated T-lymphocytes, a subset of white blood cells that are believed to be involved in the development and maintenance of ITP. Daclizumab (Zenapax®) is marketed by Roche for the treatment of transplant rejection.

Hemorrhage

Hemorrhage, or bleeding, can range from a minor to a life-threatening condition. Bleeding may be external, resulting from obvious cuts, punctures or other wounds, or it may occur internally, in which case no obvious signs will be evident. Even when not apparent, internal bleeding can constitute a critical, life-threatening situation.

Novo Nordisk is evaluating its proprietary formulation of blood coagulation factor VII **eptacog alfa** (marketed as NovoSeven®) in phase II trials for several emergency bleeding indications, including upper gastrointestinal bleeds, stem cell transplantation, intracerebral hemorrhage and trauma. NovoSeven® has been marketed for nearly a decade as a treatment for hemophilia.

Anemia

Red blood cells produced in the bone marrow transport oxygen from the lungs to cells of the body, and carbon dioxide from cells back to the lungs. Erythropoietin (EPO) is a naturally occurring protein made primarily in the kidney that stimulates the manufacture of more red blood cells, when needed. If the body loses its ability to manufacture sufficient quantities of EPO, the optimal number of red blood cells (and their oxygen-carrying component, hemoglobin) can no longer be maintained in the circulation – a condition known as anemia. This is common in patients being treated with current highly cytotoxic anticancer therapies and in patients suffering from severe renal disease.

Hematopoietic agents

Darbepoetin alfa (Amgen's Aranesp®, Nespo®), a new long-acting treatment option for anemia in patients with chronic renal failure, was launched for the first time in the E.U. and the U.S. in 2001. The introduction of darbepoetin marked the first therapeutic development in the field of anemia in the past 10 years. Darbepoetin alfa requires fewer injections than epoetin (rHuEPO), the existing standard of care, due to its nearly 3-fold longer half-life. The product was subsequently approved in both territories for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malagnancies. Kirin Brewery is developing darbepoetin (KRN-321) in Japan.

Roche is conducting phase III trials evaluating the efficacy of **epoetin beta** (NeoRecormon) for the treatment of anemia in patients undergoing radiotherapy. Epoetin beta has been marketed since 1990 for the treatment of anemia secondary to renal failure.

Amgen and Chugai are codeveloping the new-generation EPO **R-744**, also known as CERA (continuous erythropoiesis receptor activator), for the treatment of cancer-related anemia and of anemia secondary to renal failure. Phase II studies are under way for both indications.

The hematopoietic agent **garnocestim** is in phase I testing at GlaxoSmithKline. It is indicated for use in hematopoietic stem cell mobilization and for the prevention of chemotherapy-induced cytopenia.

Colony-stimulating factors

Cangene's **Leucotropin™** is a recombinant human granulocyte-macrophage colony-stimulating factor

(GM-CSF) obtained from the bacterial fermentation of *Streptomyces lividans* transformed with a genetically engineered plasmid containing the rhGM-CSF gene. The amino acid sequence of Leucotropin™ is identical to the natural molecule but it is nonglycosylated. Cangene has completed phase III testing and is preparing to file for regulatory approval of Leucotropin™ in the treatment of anemia.

Gene therapy

In March 2002, the European Commission granted marketing authorization for Dynepo™ (**epoetin delta**, gene-activated EPO) for the 15 countries of the E.U. Dynepo™ is a human EPO for the treatment of anemia related to renal disease in patients receiving dialysis, as well as in patients who have not yet undergone dialysis, to elevate and maintain red blood cell production. Dynepo™ was developed using Transkaryotic Therapies' patented gene activation technology. Under a collaborative agreement, Aventis is responsible for the development and marketing activities of Dynepo™. Clinical testing in over 1,400 dialysis and predialysis patients supported the approval of Dynepo™ as a treatment for anemia related to renal disease. Shortly after E.U. approval was granted, however, Amgen filed patent infringement suits attempting to block marketing of the product, claiming that Dynepo™ and the process for producing it infringe several U.S. and European patents held by Amgen. Although noninfringement decisions were handed down by the Court of Appeals of the U.K. in July 2002 and by the U.S. Court of Appeals in January 2003, product launch is still on hold pending resolution of this matter. The companies are also conducting phase III trials evaluating Dynepo™ in the treatment of anemia associated with cancer chemotherapy.

Iron replacement therapy

Ferumoxytol (Code 7228) is the lead product in Advanced Magnetics' development pipeline. Ferumoxytol consists of intravenously administered bioavailable iron, allowing for more efficient replenishment of the body's iron stores without the common side effects associated with oral iron supplements, as well as greater flexibility in both the administration and amount of iron that can be given to a patient in comparison to other intravenous iron replacement products currently on the market. Ferumoxytol is currently in phase II clinical studies for use in iron replacement therapy in patients with anemia. It is also in phase II clinical studies for use in magnetic resonance imaging.

Sickle cell anemia

Sickle cell anemia, an inherited blood disease that can cause episodes of severe pain, damage to vital organs and death, results from a single mutation in the gene that encodes hemoglobin (Hb). The mutant or sickled hemoglobin (HbS) does not transport oxygen to the tissues effectively and forms rod-like polymers when it gives up oxygen, causing red blood cells to become rigid and irregularly shaped. These irregular and inflexible sickled cells create blockages in the blood vessels and prevent normal blood and oxygen flow to tissues. These vessel blockages, or vaso-occlusions, characterize sickle cell anemia and are responsible for most of the severe complications of the disease.

Approximately 80,000-100,000 Americans and 4 million people worldwide suffer from sickle cell anemia. Costs associated with acute care for sickle cell anemia patients in the U.S. exceed USD 500 million annually.

Currently, there are few therapeutic options for sickle cell patients. Acute crises are treated through blood transfusions and opiates. Chronic hydroxyurea therapy is available for some individuals who frequently experience crises. Hydroxyurea has been demonstrated to reduce hospitalizations and spare patients from some crises. Unfortunately, hydroxyurea can be associated with bone marrow toxicity and other significant side effects. Moreover, the long-term effects of hydroxyurea are unknown and hence represent a significant concern for physicians, patients and regulatory authorities.

Rheologic/antithrombotic agents

CytRx's Flocor™ (**poloxamer-188**) is a novel intravascular agent that improves blood flow by lowering blood viscosity and decreasing friction between blood cells and blood vessel walls. By essentially creating a coating on the damaged cells, Flocor™ allows blood cells to "slip over" one another, profoundly improving blood flow and restoring oxygen delivery. A variety of preclinical and clinical studies suggest Flocor™ may be of significant benefit in acute vascular disorders such as stroke, heart attack and vaso-occlusive crisis of sickle cell disease. CytRx recently completed a phase III trial evaluating Flocor™ in sickle cell patients suffering from vaso-occlusive crisis. In this study involving 255 patients, Flocor™ demonstrated statistically significant efficacy in patients who were 15 years of age or less, as well as in patients who were on concomitant hydroxyurea therapy (used to help reduce the number of painful crises). Flocor™ also demonstrated a statistically significant increase in the number of treated patients who achieved crisis resolution within 7 days as compared to placebo. If approved, Flocor™ will be the only disease-modifying treatment for vaso-occlusive crisis in sickle cell disease. The U.S. FDA has granted the product orphan drug status for this indication.

Ion channel modulators

Researchers from Icagen have identified an ion channel in red blood cells that plays a significant role in ion

homeostasis and volume regulation of red blood cells. Studies indicate that blocking the flow of ions through this channel – called the intermediate conductance K(Ca) 3.1 (IKCa1) channel – prevents the loss of salt and water from these cells. This should prevent dehydration of the red blood cell, thereby preventing increases in HbS concentration and the resulting polymerization. Icagen is currently conducting phase II clinical trials evaluating the IKCa1 channel blocker **ICA-17043** for the treatment of sickle cell anemia. Preclinical and preliminary clinical results indicate that ICA-17043 has excellent efficacy and safety, inhibiting red blood cell dehydration *in vitro* and reducing the number of dense red blood cells in the sickle cell mouse model.

Antimetabolites

SuperGen has received orphan drug status from the FDA for **decitabine** (Dacogen™) for the treatment of sickle cell anemia. Decitabine was previously designated an orphan drug in myelodysplastic syndrome (MDS). SuperGen is developing decitabine for MDS, sickle cell anemia and refractory chronic myelogenous leukemia (CML), and is also evaluating its potential in solid tumors. The company is preparing a multicenter sickle cell study in the U.S. and an international thalassemia study. Decitabine's primary mechanism of action is thought to be the correction of DNA methylation. In previous clinical studies, decitabine has been shown to increase fetal hemoglobin levels in 100% of patients with sickle cell anemia.

Vertex is currently conducting phase I trials of **VX-563**, an orally active histone deacetylase inhibitor with potential in the treatment of sickle cell anemia. The company plans to complete phase I testing during the first half of 2003.

Phytopharmaceuticals

Xechem filed an application in March 2003 with the FDA seeking orphan drug designation for its phytopharmaceutical product Hemoxin™ (**NIX-0699**) for sickle cell disease. In July 2002, Xechem signed an exclusive, worldwide license for the manufacturing, marketing and distribution of Hemoxin™ (marketed as Nicosan™ in Nigeria) with the National Institute for Pharmaceutical Research and Development, Abuja, Government of Nigeria. Nicosan™ was launched in Nigeria in April 2003, and Xechem is preparing to file a U.S. IND for Hemoxin™.

Factor XIII deficiency

Factor XIII deficiency is perhaps the rarest of all clotting factor deficiencies, affecting just one in several million persons. A hallmark of this rare inherited deficiency is poor wound healing and abnormal scar formation. The reason is that factor XIII, also called fibrin stabilization factor, is necessary for clot formation and wound healing. Factor XIII is responsible for clot stabilization and cross-linking of the fibrin polymer in blood. A clot will form in the absence of factor XIII, but it will be unstable.

Factor XIII deficiency is a severe bleeding disorder usually associated with trauma. Typically, it is discovered in newborn babies who suffer recurrent bleeding from the umbilical stump and hemorrhages after circumcision. Severely affected patients have a high incidence of intracranial hemorrhage with little or no trauma. Affected women often experience spontaneous abortion unless treated with plasma replacement therapy. Bleeding in surgery is not excessive, but delayed bleeding can occur.

Deficiency of factor XIII can be corrected with infusions of fresh frozen plasma, cryoprecipitate or FXIII concentrates. Because of the high incidence of intracranial bleeding and spontaneous abortions, prophylaxis is often recommended. Minimal factor XIII activity (as little as 5%) is required to prevent bleeding complications.

Replacement therapies

ZymoGenetics is conducting a series of phase I clinical trials evaluating the safety and pharmacokinetics of escalating doses of the company's **recombinant factor XIII** (rFXIII) in healthy volunteers and in patients with congenital or acquired factor XIII deficiency. ZymoGenetics has concurrently signed a license agreement allowing it exclusive rights for rFXIII development covered by Aventis Behring patents. The agreement covers the exclusive worldwide license for the development of rFXIII as a therapeutic protein, ending a nonexclusive cross-license agreement that previously existed between the companies.

Hemophilia

Hemophilia is a potentially crippling and life-threatening congenital bleeding disorder that affects males. Approximately 200,000-300,000 males worldwide are believed to have hemophilia type A or type B. In patients with hemophilia A, production of the blood clotting protein factor VIII is absent, decreased or defective. The same kind of disturbances with another blood clotting protein, factor IX, are the cause of hemophilia B. Severe hemophilia, which typically becomes apparent in the first years of life, is characterized by spontaneous bleeding that is difficult to control. Patients with severe hemophilia may require treatment for bleeding several times per month.

Treatment for hemophilia and other coagulation factor deficiencies usually consists in replacement therapy, *i.e.*, administration of the missing clotting factor. Both plasma-derived and recombinant clotting factors have been used, although the former is associated with a significant risk of viral transmission. Development of "inhibitors", or

antibodies to replacement therapy, is a major problem that develops in approximately 30% of hemophilia A and 3-5% of hemophilia B sufferers.

Novel replacement therapies

Antihemophilic factor (recombinant), plasma/albumin-free method (**rAHF-PFM**, Advate) is a new investigational factor VIII therapy developed by Baxter in response to requests from the medical and hemophilia community. rAHF-PFM is the first factor VIII recombinant therapy to be prepared without the addition of any human- or animal-derived raw materials in the cell culture process, purification or final formulation. Advate was recently approved by the FDA for the prevention and control of bleeding episodes in subjects with hemophilia A. The product is also under regulatory review in Europe and Canada, with European approval anticipated in the second half of this year. There are several ongoing studies of Advate, including a continuation study in previously treated patients, a surgery study, a pediatric study and a study in Japanese patients required for regulatory submission in Japan. Baxter also plans to initiate a study in previously untreated patients and intends to conduct additional phase IV studies.

Ipsen's **OBI-1**, a recombinant porcine factor VIII, is being evaluated as a hemostatic enzyme for the treatment of both congenital and acquired hemophilia. Comparative studies conducted in animal models indicate that this new hemostatic agent is superior in potency to Hyate:C, the company's marketed hemophilia therapy. OBI-1 is currently in phase I clinical testing.

Gene therapy

The cloning of the genes encoding the blood clotting factors factor VIII and factor IX has spurred research initiatives in the field of gene therapy for hemophilia. Avigen is currently conducting a phase I/II safety study with its adeno-associated virus (AAV) vector containing the gene for human coagulation factor IX (**AAV-hFIX**, Coagulin-B®). This is an open-label, nonrandomized study that will enroll approximately 10 patients. The primary purpose of the study is to assess the safety of 3 different doses of AAV-hFIX. Each dose level will also be evaluated for activity. The AAV vector will be infused into the liver through the hepatic artery using a procedure called angiography. Patients are actively being enrolled in this study. Interim data on the first 6 patients treated were presented in December 2002 at the annual meeting of the American Society of Hematology.

Transkaryotic Therapies has completed a preliminary phase I study of **TKT-Factor VIII**, a gene therapy for the treatment of hemophilia A. The study, which was published in 2001 in the New England Journal of Medicine, demonstrated that the nonviral *ex vivo* gene therapy system delivering factor VIII to patients with severe hemophilia A was safe and well tolerated over 1 year of monitoring in the first 6 treated patients. The report also provided evidence that the delivery of factor VIII using TKT's nonviral gene therapy system may be a practical treatment option for this patient population and may be effective in reducing the occurrence of spontaneous bleeding in patients with severe hemophilia. Due to financial constraints leading to company reorganization and downsizing, this product has been made available for licensing.

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a chronic disease in which a patient's oxygen-carrying red blood cells carry a complement inhibitor deficiency, and as such are abnormally fragile and inadvertently destroyed by normal complement activation. The disorder is caused by a mutation in certain types of adult blood cells. Because of this mutation, certain types of proteins, including complement inhibitors, are unable to attach to the surface of the cell. More specifically, the PNH mutation prevents the assembly of a glycosyl-phosphatidylinositol (GPI) anchor, a necessary step in surface attachment of some proteins. Consequently, several proteins with this GPI anchor are diminished or absent, 2 of which are crucial in protecting blood cells from inappropriate complement destruction. Without these two protective proteins, PNH red blood cells, in particular, are easily burst by complement, resulting in anemia, fatigue, bouts of dark-colored urine and various other complications. PNH is frequently associated with other disorders of blood cell production including aplastic anemia and other forms of bone marrow failure. Approximately 5,000-10,000 U.S. patients suffer from the disorder.

Complement inhibitors

Alexion's **eculizumab** is a protein-based drug that blocks the C5 component of the complement system, thereby preventing the final stages of complement activation. In laboratory tests, eculizumab completely blocked complement-mediated red blood cell destruction. As a result, it is possible that treatment with eculizumab could block the complement-mediated destruction of PNH red blood cells and therefore alleviate most symptoms associated with the disease. Eculizumab will not be a cure for PNH, but it does have the potential to improve quality of life through reduction in disease symptoms. In December 2002, Alexion announced preliminary results of its phase Ib clinical trial using eculizumab in hemolytic transfusion-dependent PNH patients.

Blood substitutes

Blood transfusions have been used to save lives since the 1900s, although the emergence of AIDS in the 1980s,

Table IV: Development of new blood substitutes and blood components.

Product Name	Source	Description	Status (indication)
Hemoglobin glutamer-250 (Hemopure®)	Biopure	Hemoglobin-based oxygen carrier	Launched-2002 (anemia)
Hemoglobin raffimer (Hemolink™)	Hemosol	Crosslinked oligomerized human hemoglobin	Prereg. (CABG surgery)
Polynitroxylated hemoglobin (Hemozyme)	SynZyme	Hemoglobin-based oxygen carrier	Phase III (surgery and hemorrhagic shock)
Oxygent™	Alliance/Baxter	Perflubron emulsion	Phase III (surgery)
Pyridoxalated hemoglobin polyoxyethylene (PHP)	Curacyte	Natural human hemoglobin	Phase III (distributive shock)
PolyHeme®	Northfield Labs	Purified hemoglobin derived from human blood	Phase II (trauma)
Hemospan™	Sangart	Hemoglobin-based oxygen carrier containing natural human hemoglobin combined with poly(ethylene glycol)	Phase Ib/II (surgery)
PentaLyte®	BioTime	Blood plasma volume expander	Phase I (hypovolemia)
Oxycyte™	Synthetic Blood International	Perfluorocarbon-based blood substitute and therapeutic oxygen carrier	IND filed (stroke, myocardial infarction, malignant diseases)

as well as the perpetual shortage of donor blood and concomitant concerns about other blood-borne diseases, have led to increased interest in the development of viable alternatives to human blood for transfusion. Safe and effective blood substitutes are now available for certain applications, although they are still not ready for routine clinical use. Better blood substitutes are still needed.

Northfield Laboratories, one of the pharmaceutical companies that is actively involved in the development of new blood substitutes, estimates that approximately 14 million units of blood were transfused in the U.S. alone during the year 2001. Approximately 8.5 million of these units were administered to patients suffering the effects of acute blood loss (*e.g.*, trauma, surgery or unexpected blood loss), while the remainder was administered to patients with chronic anemia or in connection with general medical applications.

In 2002, South Africa became the first market worldwide for Biopure's Hemopure® (**hemoglobin glutamer-250 bovine**, HBOC-201) to eliminate, delay or reduce the need for allogeneic red blood cells in adult surgical patients who are acutely anemic. The marketing application was supported by data from 20 human clinical trials conducted over the past 9 years in the U.S., Europe, South Africa and Canada. The South African approval marks the first time that an oxygen therapeutic, a new class of intravenously administered pharmaceutical, has been approved for human use. Oxygen therapeutics can be used to deliver oxygen to the body's tissues as a sterile alternative to red blood cell transfusion. In October 2002, the U.S. Food and Drug Administration accepted for review Biopure's Biologic License Application to market Hemopure® in the U.S. for a similar indication in orthopedic surgical patients. This acceptance is the first time a hemoglobin-based oxygen therapeutic for human use has reached this stage in the U.S. regulatory process.

Table IV presents information on new blood substitutes and blood components in active development, together with their targeted indications and status of development.

Information sources on the internet

American Society of Hematology
www.hematology.org

American Thrombosis Association
www.bloodclot.org

National Hemophilia Foundation
www.hemophilia.org

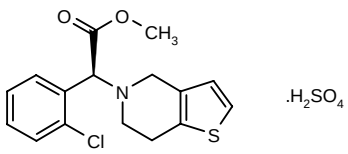
Thrombosis Online
www.thrombosisonline.com

Thrombosis Research Institute
www.tri-london.ac.uk

Monograph Updates of Drugs for Hematological Disorders

N.E. Mealy,
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

Clopidogrel Hydrogensulfate



The antiplatelet agent clopidogrel hydrogensulfate, aP2Y$_{12}$ (P2T) receptor antagonist, was discovered by Sanofi-Synthélabo, and is developed and marketed worldwide by Sanofi-Synthélabo and Bristol-Myers Squibb as Plavix® and Iscover®. It was originally approved for reducing atherosclerotic events (myocardial infarction, stroke, death due to vascular causes) in patients with a history of symptomatic atherosclerotic disease defined by recent ischemic stroke, recent myocardial infarction or established peripheral arterial disease.

Since last year's review, the European Commission has approved clopidogrel in the E.U. for the new indication of the prevention of atherothrombotic events in patients suffering from non-S-T segment elevation acute coronary syndrome (unstable angina or non-Q wave myocardial infarction) in combination with acetylsalicyclic acid (ASA). Clopidogrel was approved in the U.S. in February 2002 for the treatment of acute coronary syndrome (ACS). The approval is based on the results of the CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) study which enrolled 12,562 patients with acute coronary syndrome (ACS) and compared clopidogrel to placebo, with both groups also receiving ASA. Clopidogrel plus ASA significantly reduced the risk of heart attack, stroke or cardiovascular death by 20% (9.3% *vs.* 11.4% on placebo) in patients with ACS. The reduction of atherothrombotic events was demonstrated with early treatment with clopidogrel and the benefit was sustained with prolonged treatment for up to 1 year. The benefits of clopidogrel outweighed the risk of bleeding seen with the drug. When patients were stratified according to their cardiovascular event risk (TIMI scores), an increasing risk was found to be associated with an increased incidence of cardiovascular death, myocardial infarction or stroke and the benefits of clopidogrel were consistent across risk groups. Clopidogrel continues to be investigated in an extensive international development program: in the CREDO (Clopidogrel for the Reduction of Events During Observation) study for patients with coronary angioplasty, in the COMMIT (Clopidogrel and Metoprolol Myocardial Infarction Trial) and CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy) studies in patients with acute myocardial infarction, in the MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke) neurological study, in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) study in patients at high risk of atherothrombotic events, in the ACTIVE (Atrial Fibrillation Clopidogrel Trial with Irbesartan for the Prevention of Vascular Events) study for patients with atrial fibrillation, and in the CASPAR (Clopidogrel and Aspirin in Bypass Surgery for Peripheral Arterial Disease) and CAMPER (Clopidogrel and Aspirin in the Management of Peripheral Endovascular Revascularization) studies for patients with peripheral arterial disease (1-8).

The Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events (PCI-CURE) study conducted in 2,658 patients with unstable angina reported that the combination of

Table I: Clinical studies of clopidogrel hydrogensulfate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Unstable angina pectoris, myocardial infarction	Randomized double-blind multicenter	Clopidogrel, 300 mg/d → 75 mg/d + Aspirin, 75-325 mg x 3-12 mo (n=6259) Placebo x 3-12 mo + Aspirin, 75-325 mg (n=6303)	12,562	The benefits of clopidogrel treatment outweighed the increased risk of bleeding and was effective in reducing ischemic events and the risk of cardiovascular death in patients with acute coronary syndromes	9
Myocardial infarction	Randomized, open	Clopidogrel, 75 mg/d x 6 mo Aspirin, 75 mg/d x 6 mo	184	Clopidogrel significantly reduced the thrombotic risk factors and C-reactive protein levels after myocardial infarction	11
Coronary angioplasty, myocardial infarction	Open	Aspirin, 325 mg po + Clopidogrel, 300 mg po + Enoxaparin, 0.5 μg/kg iv + Eptifibatide, 180 μg/kg iv bolus → 2 μg/kg/min infusion over 10 min → 180 mcg/kg iv bolus	198	Administration of aspirin, clopidogrel, enoxaparin and eptifibatide just before percutaneous coronary intervention was feasible and safe in patients with acute coronary syndromes	13
Coronary angioplasty, stenting	Retrospective	Aspirin + Clopidogrel	354	The combination of aspirin plus clopidogrel was well tolerated and effective in preventing thrombotic complications after elective angioplasty and stenting	14
Athero-sclerosis, myocardial infarction, ischemic stroke	Randomized	Clopidogrel x 1-3 y Aspirin x 1-3 y	19,185	Clopidogrel provided broadly effective prophylaxis for acute myocardial infarction in patients with atherothrombosis	15
Coronary angioplasty, myocardial infarction	Open	Clopidogrel, 375 mg + Aspirin, 75 mg/d (n=706) Aspirin, 75 mg/d (n=724)	1,430	Clopidogrel was safe and effective for cardiac event prophylaxis in patients undergoing percutaneous coronary interventions	16
Angina pectoris	Open	Clopidogrel, 75 mg/d po + Aspirin, 325 mg/d po + 192Ir (ribbon seeds), 14 Gy to 2 mm x 6 or 12 mo	120	The clopidogrel plus aspirin combined 12-month regimen was more effective than the 6-month regimen in reducing major cardiac events and in increasing target-lesion revascularization rate in patients with in-stent restenosis	17
Coronary angioplasty, coronary artery disease		Abciximab, 0.25 mg/kg bolus iv → 0.125 μg/kg/min infusion Tirofiban, 10 μg/kg iv bolus → 0.15 μg/kg/min infusion Eptifibatide, 180 μg/kg iv bolus → 2 μg/kg/min infusion	503	In patients undergoing percutaneous coronary interventions, the incidence of bleeding was not correlated with degree of platelet inhibition, but it was strongly correlated with the degree of anticoagulation, with peak activated clotting time predicting bleeding complications	18

clopidogrel and aspirin was better than aspirin alone in reducing the risk of cardiovascular death and myocardial infarction after PCI (9). The results of this study and some that follow are summarized in Table I.

Two case studies undertaken to evaluate the effects of clopidogrel in heart transplantation patients found that adjunctive administration of the drug (75 mg/day) to existing therapy was implicated in the onset of acute rhabdomyolysis, which was reversed following discontinuation. The drug may adversely affect the metabolism of other drugs and should therefore be used with caution in this type of clinical situation (10).

The randomized CADET trial evaluated treatment with clopidogrel or aspirin beginning 3-7 days after a myocardial infarction in 184 patients. The dose of both drugs was 75 mg/day which was given for 6 months. Similar significant reductions in thrombotic risk factors (Clauss fibrinogen, immunonephelometric fibrinogen, fibrin D-dimer, von Willebrand factor, factor VIII activity) and C-reactive protein were seen with the treatments (11).

In 90 patients with cerebral vascular disease or coronary artery disease, administration of clopidogrel 75 mg/day for 12 weeks significantly reduced ADP-induced platelet aggregation and prolonged bleeding time. The drug was also safe and did not affect plasma fibrinogen concentrations (12).

In a pilot study, 198 patients with ACS received aspirin (325 mg p.o.), clopidogrel (300 mg p.o.), enoxaparin

(0.5 μg/kg i.v.) and eptifibatide (180 μg/kg by i.v. bolus and 2 μg/kg/min by continuous infusion followed by another 180 μg/kg by bolus) just prior to PCI. Follow-up for 30 days revealed the treatment regimen to be feasible and safe in this setting (13).

A retrospective study assessed the safety profile of a combination of aspirin and clopidogrel in 354 patients who underwent elective angioplasty and stenting of the cerebral arteries. There were 4 ischemic strokes and 3 deaths, and another 17 patients experienced complications potentially attributable to failure or excess of the antiplatelet therapy. The authors concluded that the combination of aspirin and clopidogrel was effective in the prevention of occlusive complications after angioplasty and stenting of cerebral arteries (14).

Clopidogrel reduced the risk of acute myocardial infarction from 5.04% seen with aspirin to 4.2% after follow-up of 1-3 years in the 19,185 patients with symptomatic atherothrombosis enrolled in the CAPRIE (Clopidogrel *versus* Aspirin in Patients at Risk of Ischemic Events) trial. The risk reduction was seen in both high- and low-risk patients (15).

Aspirin and clopidogrel 375 mg were administered to 706 consecutive patients undergoing PCI and outcomes were compared with a control group of 724 patients receiving only aspirin. Occurrence of the composite endpoint (death, myocardial infarction or urgent revascularization) was reduced from 8.2% to 4.8% with clopidogrel treatment, which was safe and reduced costs compared with aspirin alone (16).

In the Washington Radiation for In-Stent Restenosis Trial-12 (WRIST-12), 120 patients with in-stent restenosis underwent PTCA, laser ablation or rotational atherectomy and a ribbon with radioactive 192Ir seeds was delivered to the treated site. A radiation dose of 12 Gy to 2 mm was used. After the intervention, patients were given clopidogrel 75 mg/day for 12 months and life-long aspirin (325 mg/day) treatment. Comparison at 15 months with the WRIST PLUS trial, in which clopidogrel was given for 6 months, showed that the longer clopidogrel therapy reduced the major cardiac event and target lesion revascularization rates to a greater extent (17).

In the GOLD study, 503 patients undergoing PCI were treated with abciximab, tirofiban or eptifibatide. A review of data from this study found that the incidence of bleeding complications was not correlated with the degree of platelet inhibition but was strongly correlated with the degree of anticoagulation (18).

1. Fox, K.A.A., Mehta, S.R., Zhao, F., Gersh, B., Yusuf, S. *The risks versus benefits of clopidogrel treatment in acute coronary syndrome patients overall, and those undergoing CABG: The CURE trial*. Eur Heart J 2002, 23(Suppl.): Abst 2691.

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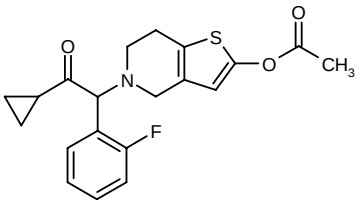
CS-747



The antiplatelet agent CS-747, a P2T ($P2Y_{12}$) receptor antagonist like clopidogrel, is now in phase II trials as a treatment for stroke and acute coronary syndromes. Originally discovered by Ube and subsequently licensed to Sankyo, it is being developed in conjunction with Lilly (1).

A recent study demonstrated the antiplatelet efficacy of CS-747 in rat models of cerebral arterial thrombosis (*i.e.*, photoirradiation to the middle cerebral artery), cerebral embolism (*i.e.*, photochemically induced endothelial injury) and peripheral arterial occlusive disease. In the thrombosis model, CS-747 (3 and 10 mg/kg p.o. 4 h before irradiation) significantly and dose-dependently decreased thrombosis-induced cerebral infarction at 24 h postirradiation; clopidogrel (30 mg/kg p.o.) had no significant effect. CS-747 (0.3-3 mg/kg p.o.) was also effective in the embolism model, where it dose-dependently reduced the incidence, total area and number of cerebral infarcts at 24 h postinjury; clopidogrel (10 mg/kg p.o.) was 10 times less effective in this model. Moreover, the progression of lauric acid-induced peripheral arterial occlusive disease was dose-dependently inhibited with CS-747 pretreatment (0.03-3 mg/kg/day p.o. starting the day before lauric acid injection and continuing for 11 days). Clopidogrel (3-30 mg/kg/day) and ticlopidine (100 mg/kg/day) were also effective in this model, but less potent than CS-747. From these results, it was concluded that CS-747 may be a potential candidate for the prevention of arterial occlusive diseases (2).

In a rat arteriovenous shunt thrombosis model, a combination of oral CS-747 (0.3 and 0.6 mg/kg) and oral aspirin (10 mg/kg) was more effective than either drug alone in preventing thrombosis and had no effects on the bleeding time of the animals. The combination therapy did not enhance the inhibition of ADP-induced platelet aggregation by CS-747, but increased the inhibition of collagen-induced platelet aggregation. These effects were confirmed by *ex vivo* studies in dogs, where the combination potently inhibited platelet aggregation induced by collagen and epinephrine (3).

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Darbepoetin Alfa

Darbepoetin alfa (Aranesp®, Nespo®), previously known as novel erythropoiesis-stimulating protein, or NESP, is a recombinant erythropoietic protein with superior *in vivo* activity compared to recombinant human erythropoietins (rHuEPO) such as epoetin alfa. It was launched by Amgen in 2001 in Europe and the U.S. for the treatment of anemia associated with chronic renal failure, and was subsequently approved in both markets for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies (1-3).

The alleviation of anemia of chronic disease by darbepoetin alfa (3-6 mg/kg twice monthly) and pegsunercept (4 mg/kg 3 times weekly) was investigated in a rat model of relapsing arthritis. Combined therapies significantly enhanced hemoglobin levels, induced more reticulocytes and red blood cells, and increased total serum iron concentration, corpuscular volume and corpuscular hemoglobin in a synergistic manner as compared to monotherapies (4).

Female BDF1 mice were used as a model of erythroid response to compare the pharmacological properties of darbepoetin alfa and rHuEPO. Hemoglobin levels increased more and showed less fluctuation with darbepoetin alfa than with equivalent doses of rHuEPO, both as a single bolus and as multiple-dose injections at regular intervals (5).

The pharmacokinetics and pharmacodynamics of rHuEPO (epoetin) were compared with darbepoetin alfa in 47 patients with chronic kidney disease receiving hemodialysis. No significant differences in the safety profiles of the agents were observed. The $t_{1/2}$ of darbepoetin alfa was between 2 and 3 times longer and clearance approximately 4 times greater at 1 and 12 weeks and at hemoglobin steady state. Darbepoetin alfa pharmacoki-

netics were independent of dose and time and mean hemoglobin values at steady state for both agents were within the target range (6).

Pediatric patients with chronic kidney disease were administered a single dose of darbepoetin alfa (0.5 μg/kg) intravenously or subcutaneously in a randomized, 2-way crossover study. Pharmacokinetic parameters following i.v. *versus* s.c. administration were: $t_{1/2}$ = 22.1 ± 4.8 h *vs.* 42.8 ± 23.0 h; AUC = 233 ± 56 ng·h/ml *vs.* 122 ± 20 ng·h/ml; and clearance = 2.3 ± 0.6 ml/h/kg *vs.* 4.3 ± 0.6 ml/h/kg, respectively. Following s.c. administration, mean bioavailability was 54%. The results are similar to previous findings in adult patients, although absorption appeared to be slightly faster in pediatric patients following s.c. administration (7).

Patients with nonmyeloid malignancies (n=810) receiving or not receiving chemotherapy were enrolled in 4 studies evaluating the pharmacokinetics of darbepoetin alfa and the relationship with chemotherapy. In these studies, it was found that multiple dosing once every 1, 2 or 3 weeks did not lead to accumulation of darbepoetin alfa, which demonstrated dose-linear and time-invariant pharmacokinetics. In addition, darbepoetin alfa and endogenous erythropoietin serum concentrations increased with chemotherapy (8).

A randomized, placebo-controlled study evaluated the administration of darbepoetin alfa 4.5, 6.75, 9 or 12 μg/kg every 3 weeks or placebo to anemic patients receiving cyclic chemotherapy for solid tumors. Given once every 3 weeks, darbepoetin alfa was clinically effective and well tolerated (9).

In Part A of a 2-part study in patients with anemia and solid tumors receiving multicycle chemotherapy, 60 patients were randomized to rHuEPO 150 U 3 times weekly and 228 patients to darbepoetin alfa 1.5, 2.25 and 4.5 μg/kg once weekly. In Part B, 35 patients received rHuEPO 40,000 U once weekly and 141 patients were given darbepoetin alfa 3, 5 and 9 μg/kg every 2 weeks. The less frequent but equal total dose regimen of darbepoetin alfa examined in Part B was as effective as the once-weekly regimen studied in Part A (10).

Darbepoetin alfa was compared to epoetin alfa in 99 anemic patients with solid tumors receiving chemotherapy. In the 12-week study, patients were given either epoetin alfa 40,000 U/week (dose could be increased to 60,000 U/week) or 1 of 3 darbepoetin alfa doses: 4.5 mg/kg/week given until hemoglobin was > 1 g/dl, followed by 15 μg/kg/week; 4 loading doses of 4.5 μg/kg/week followed by 8 doses of 2.25 μg/kg/week; or 4 loading doses of 4.5 μg/kg/week followed by 4 doses of 3.0 μg/kg every 2 weeks. At the end of the study, patients given darbepoetin alfa had better fatigue and physical well-being scores and greater changes in hemoglobin than those given epoetin alfa (11, 12). The results of this study and some that follow are summarized in Table II.

The feasibility of administering darbepoetin alfa with each chemotherapy cycle was analyzed in a population of 414 cancer patients who were randomized to receive either placebo or one of several doses of darbepoetin alfa with a frequency similar to that used in most chemotherapy regimens (*i.e.*, once every 3 or 4 weeks). Both dose schedules produced hematopoietic response rates that ranged between 51% and 71% (once every 3 weeks) and between 65% and 73% (once every 4 weeks), depending on the dose administered. All doses were well tolerated and the incidence of injection-site pain was below 5% in all treatment groups (13).

A double-blind study randomized anemic cancer patients with nonmyeloid malignancies not receiving chemotherapy to either placebo or various darbepoetin alfa dose regimens, with doses ranging from 1.0-10.0 μg/m^2 administered once weekly or once every 3 or 4 weeks. All schedules were well tolerated and gave a hematopoietic response rate of up to 100%, with no sign of reduced efficacy with longer dose intervals (14).

An open-label, dose-escalation study and a placebo-controlled, double-blind trial showed that in anemic patients with cancer not currently receiving chemotherapy or radiotherapy, darbepoetin alfa increased hemoglobin when given every week, every 3 weeks or every 4 weeks. In the first study, s.c. doses of 0.5, 1.0, 2.25 and 4.5 μg/kg/week were given for 12 weeks. The double-blind study evaluated doses of 6.75 μg/kg given every 3 weeks and 6.75 or 10 μg/kg given every 4 weeks for 12 weeks. The once-weekly schedule was the most effective (15).

Darbepoetin alfa produced dose-related increases in hemoglobin in patients with anemia and cancer treated either every week or every 2 weeks in a randomized trial. Patients were initially treated for 12 weeks with darbepoetin alfa 0.5-8 μg/kg/week or epoetin alfa 150 U/kg 3 times weekly. Patients were then randomized to 12 weeks of treatment with darbepoetin alfa 3-9 mcg/kg every 2 weeks or epoetin alfa 40,000 U/week. Adverse events were similar with darbepoetin alfa and epoetin alfa (16).

An open-label clinical trial determined the effects of once-monthly darbepoetin alfa in the treatment of anemia in patients with chronic kidney disease. Patients with a baseline mean hemoglobin level of 10-12 g/dl, creatinine clearance of 15-40 ml/min and receiving stable therapy with darbepoetin alfa once every 2 weeks were included in the study. The initial drug dose was twice the dose the patients were receiving every 2 weeks at the time of inclusion, and this was titrated throughout the study in order to maintain hemoglobin levels of 10-12 g/dl. An interim analysis conducted after 11 weeks of treatment showed that all patients were successfully maintaining stable hemoglobin levels and had experienced no changes in the safety profile of the drug (17).

A retrospective study compared the efficacy of darbepoetin administered subcutaneously or intravenously to hemodialysis patients with end-stage renal disease. A total of 60 patients who were being treated with s.c. erythropoietin were switched to i.v. darbepoetin. At 6 months after changing therapy, the average percentage of patients achieving a target hemoglobin level of 11 g/dl each month had decreased from 85.2% to 68.2% with i.v. darbepoetin. This suboptimal response resulted in

Table II: Clinical studies of darbepoetin alfa (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Anemia in cancer	Randomized	Darbepoetin alfa, 4.5 µg/kg/wk [until hemoglobin >/=1 g/dl] → 1.5 µg/kg/wk 12 wk [total] Darbepoetin alfa, 4.5 µg/kg/wk x 4 wk → 2.25 µg/kg/wk x 8 wk Darbepoetin alfa, 4.5 µg/kg/wk x 4 wk → 3.0 mg/kg q2 wk x 8 Epoetin alfa, 40,000 U/wk x 12 wk [uptitrated to 60,000 U if needed]	99	The administration of darbepoetin alfa resulted in lower fatigue scores, higher physical well being scores and greater changes in hemoglobin than epoetin alfa in patients with solid tumors and anemia undergoing chemotherapy	11, 12
Anemia in cancer	Randomized, double-blind	Darbepoetin alfa, 4.5 µg/kg 1x/3 wk Darbepoetin alfa, 6.75 µg/kg 1x/3 wk Darbepoetin alfa, 9 µg/kg 1x/3 wk Darbepoetin alfa, 12 µg/kg 1x/3 wk Darbepoetin alfa, 13.5 µg/kg 1x/3 wk Darbepoetin alfa, 15 µg/kg 1x/3 wk Darbepoetin alfa, 9 µg/kg 1x/4 wk Darbepoetin alfa, 12 µg/kg 1x/4 wk Darbepoetin alfa, 15 µg/kg 1x/4 wk Darbepoetin alfa, 18 µg/kg 1x/4 wk Placebo	414	Darbepoetin was safe and effective when administered once every 3 or 4 weeks in anemic cancer patients	13
Anemia in cancer	Randomized	Darbepoetin alfa, 1.0 µg/kg 1x/wk x 12 wk (n=33) Darbepoetin alfa, 2.25 µg/kg 1x/wk x 12 wk (n=33) Darbepoetin alfa, 4.5 µg/kg 1x/wk x 12 wk (n=30) Darbepoetin alfa, 6.75 µg/kg 1x/3 wk x 12 wk (n=21) Darbepoetin alfa, 6.75 µg/kg 1x/4 wk x 12 wk (n=21) Darbepoetin alfa, 10.0 µg/kg 1x/4 wk x 12 wk (n=22) Placebo (n=22)	182	Darbepoetin alfa was well tolerated and induced hematopoietic response rates up to 100% in cancer patients with chronic anemia	14
Anemia in cancer	Randomized, double-blind	Darbepoetin alfa, 0.5 µg/kg 1x/wk sc x 12 wk (n=6) Darbepoetin alfa, 1 µg/kg 1x/wk sc x 12 wk (n=33) Darbepoetin alfa, 2.25 µg/kg 1x/wk sc x 12 wk (n=33) Darbepoetin alfa, 4.5 µg/kg 1x/wk sc x 12 wk (n=30) Darbepoetin alfa, 6.75 µg/kg sc 1x/3 wk x 12 wk (n=21) Darbepoetin alfa, 6.75 µg/kg sc 1x/3 wk x 12 wk (n=21) Darbepoetin alfa, 10 µg/kg sc 1x/4 wk x 12 wk (n=22) Placebo (n=22)	188	Darbepoetin alfa was equally effective when given every week, every 2 weeks and every 3 weeks in anemic cancer patients	15
Anemia in cancer	Randomized, open, multicenter	Darbepoetin alfa, 0.5 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 1 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 1.5 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 2.25 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 4.5 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 6 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 8 µg/kg 1x/wk sc x 12 wk Darbepoetin alfa, 3 µg/kg sc 1x/2 wk x 12 wk Darbepoetin alfa, 5 µg/kg sc 1x/2 wk x 12 wk Darbepoetin alfa, 7 µg/kg sc 1x/2 wk x 12 wk Darbepoetin alfa, 9 µg/kg sc 1x/2 wk x 12 wk Epoetin alfa 40,000 U 3x/wk sc [initial dose] x 12 wk Epoetin alfa, 150 U/kg sc 3x/wk [initial dose] x 12 wk	429	Darbepoetin alfa was safe and effective in treating anemia in cancer patients receiving chemotherapy	16

Continuation

Table II (Cont.): Clinical studies of darbepoetin alfa (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Anemia in chronic renal failure	Open	Darbepoetin, 1x/mo x 27 wk		An interim analysis conducted after 11 weeks of treatment showed that all patients were successfully maintaining stable hemoglobin levels. No changes were found in the safety profile of darbepoetin alfa after switching to a once-monthly dosing regimen	17
Anemia in hemodialysis and chronic renal failure	Retrospective	Darbepoetin alfa	48	The administration darbepoetin alfa for 5 months increased average hemoglobin levels and the percentage of patients achieving target hemoglobin levels. No significant changes were found in the average monthly dose of the drug, although the patients tended to switch from a once-weekly to a once-monthly dosing pattern	18
Anemia in hemodialysis and chronic renal failure	Open	Darbepoetin iv x 6 mo Darbepoetin sc x 6 mo	60	Switching from subcutaneous erythropoietin to intravenous darbepoetin reduced the average percentage of patients who achieved a target hemoglobin level of 11 g/dl. This suboptimal response justified switching to s.c. darbepoetin, which increased the average percentage of patients achieving the target hemoglobin level after 6 months	19
Anemia in kidney transplantation	Retrospective	Darbepoetin alfa + Concomitant medications	36	Darbepoetin alfa was well tolerated and allowed renal transplant patients with anemia to reach a hemoglobin concentration equal to or higher than 12 g/dl	20
Anemia in renal failure	Pooled/meta-analysis	Darbepoetin alfa, 0.75 μg/kg/wk [starting dose] iv or sc 1-3 x/wk Darbepoetin alfa, 0.045 μg/kg/wk [starting dose] iv or sc 1-3x/wk Darbepoetin alfa, 0.225 μg/kg/wk [starting dose] iv or sc 1-3x/wk	122	Darbepoetin alfa was safe and effectively raised hemoglobin levels in patients with anemia and chronic kidney disease	21
Healthy Volunteers	Randomized	Darbepoetin alfa, 3 μg/kg sc (n=10) Darbepoetin alfa, 6.5 μg/kg sc (n=10)	20	A single subcutaneous dose of darbepoetin alfa 6.5 mg/kg effectively increased the hemoglobin levels of healthy volunteer	22
Anemia in renal failure	Randomized, double-blind	Darbepoetin alfa, 1x/wk x 28 wk [dose titrated according to hemoglobin levels] (n=169) Epoetin, iv 3x/wk x 28 wk [dose titrated according to hemoglobin levels] (n=335)	504	The reduced dosing schedule of darbepoetin alfa maintained hemoglobin concentrations as effectively as epoetin and with similar safety in patients with chronic kidney disease and anemia	24

switching patients to receive s.c. darbepoetin, and as a result, the average percentage of patients achieving the target hemoglobin level increased to 82.7% each month (18, 19).

The safety and efficacy of darbepoetin alfa in renal transplant recipients suffering from anemia were assessed in a retrospective study that included data from 36 patients. The administration of an average darbepoetin alfa dose of 0.47 mg/kg resulted in 28 patients reaching the target hemoglobin level of 12 g/dl. There were no drug-related adverse events, and only 1 case of acute rejection was reported (20).

Darbepoetin alfa was examined as a treatment for anemia in diaylsis patients in 2 multicenter, randomized studies. Darbepoetin alfa was given intravenously to 75 hemodialysis patients and subcutaneously to 47 patients receiving peritoneal dialysis. Doses studied were 0.075-0.75 μg/kg/week once weekly or 3 times per week;

the drug was administered for up to 52 weeks in patients with an increase of at least 1 g/dl in hemoglobin after 4 weeks. In both studies, dose-related increases in hemoglobin were seen, and a weekly starting dose of 0.45-0.75 μg/kg/week was optimal (21).

The efficacy of darbepoetin alfa for increasing preoperative hemoglobin levels prior to surgery and thus reducing the need for blood transfusion after surgery was evaluated in a phase I clinical trial conducted in healthy elderly subjects. Administration of a single s.c. dose of 6.5 μg/kg of darbepoetin alfa increased hemoglobin levels by 1.59 g/dl for 21 days. In contrast, a dose of 3 μg/kg was suboptimal, increasing hemoglobin levels by 0.93 g/dl for 21 days (22).

The efficacy and safety of darbepoetin alfa in the treatment of renal anemia associated with dialysis were compared with rHuEPO in a multicenter, randomized, open-label study. A total of 522 patients were included and, after a 4-week screening phase during which they were treated with rHuEPO, they were randomized to receive either rHuEPO at the same dose, schedule and route of administration (i.v. or s.c.) or darbepoetin alfa at the same dose but at reduced frequency for 52 weeks. Both treatments were safe and effectively maintained or slightly increased the hemoglobin levels of the patients, No significant differences between the treatments were found for efficacy, incidence of adverse events or death rate; the most common adverse events were hypotension, myalgia and hypertension, and significant differences were found only for pruritus and back pain (with incidence rates of 14% and 10%, respectively, for darbepoetin alfa, and 5% and 16% for rHuEPO, respectively). These results confirm that darbepoetin alfa is as effective as rHuEPO with less frequent administration (23).

In a randomized, double-blind study, 507 patients with chronic kidney disease and anemia receiving epoetin continued i.v. epoetin 3 times/week or were switched to i.v. darbepoetin alfa given once weekly. Treatment lasted 28 weeks during which doses were titrated according to hemoglobin concentrations. The reduced dosing schedule of darbepoetin alfa was found to maintain hemoglobin concentrations as effectively as epoetin, with similar safety (24).

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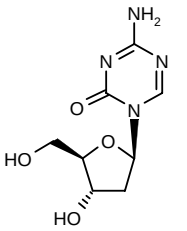
Decitabine



SuperGen has received orphan drug status from the FDA for decitabine (Dacogen™) for the treatment of sickle cell anemia. Decitabine was previously designated an orphan drug in myelodysplastic syndrome (MDS). SuperGen is developing decitabine for MDS, sickle cell anemia and refractory chronic myelogenous leukemia (CML), and is evaluating its potential in solid tumors. The company is preparing a multicenter sickle cell study in the U.S. and an international thalassemia study. Decitabine's primary mechanism of action is thought to be the correction of DNA methylation. In previous clinical studies, decitabine has been shown to increase fetal hemoglobin levels in 100% of patients with sickle cell anemia (1).

A 36-week study of decitabine showed that treatment resulted in significantly elevated fetal hemoglobin levels in 100% of sickle cell anemia patients taking part. The trial enrolled 7 patients, 5 of whom had shown no response to hydroxyurea, the current standard of care. One of the enrolled patients had SS/α-thalassemia, a rare form of sickle cell anemia. All 7 patients receiving decitabine (starting dose of 0.3 mg/kg/day by i.v. infusion 5 days a week for 2 weeks, followed by a 4-week rest period) experienced on average a 4-fold elevation in levels of fetal hemoglobin, which prevents sickle-shaped cells from congregating. The starting dose was reduced to 0.25 mg/kg after the first cycle due to decreases in the absolute neutrophil count. There was no cumulative toxicity seen after up to 9 months of treatment. This may permit shorter intervals between drug treatments, potentially leading to higher total hemoglobin and fetal hemoglobin levels after several treatment cycles. There was a lack of increase in total hemoglobin for the patient with SS/α-thalassemia, although this was not unexpected as this condition generally signifies less severe disease (2).

Decitabine was administered to 8 patients with sickle cell disease at a dose of 0.2 mg/kg twice weekly for 6 weeks and, after a 2-week rest period, 1-3 times a week for a further 6 weeks. Decitabine was found to reduce adhesion of sickle red blood cells to thrombospondin-1 and laminin *in vitro*. Fibrin D-dimer levels also decreased, as did those of soluble VCAM-1. These findings indicated that decitabine can reduce vascular pathologies in patients with sickle cell disease (3).

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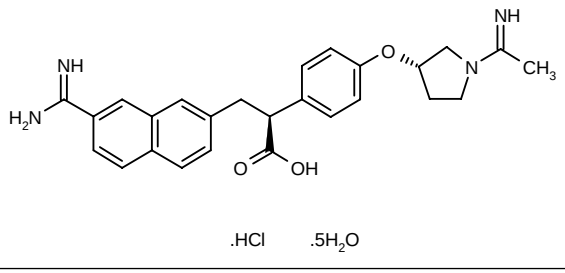
DX-9065a



.HCl .5H_2O

The synthetic, low-molecular-weight factor Xa inhibitor DX-9065a is presently in phase II trials at Daiichi Pharmaceutical for thrombotic complications.

The effect of DX-9065a (200-800 ng/ml) on tissue factor pathway inhibitor (TFPI) release was investigated in human umbilical vein endothelial cells incubated with increasing concentrations of the drug. The resulting

stimulation of TFPI release suggested that the factor Xa-antagonist activity of the drug involves both direct molecular binding and the formation of endothelium-mediated protease-antiprotease complexes (1).

A study to compare the inhibitory effects of DX-9065a and argatroban in extrinsically triggered human citrated plasma found that argatroban demonstrated a greater suppressive effect on endogenous thrombin, particularly at elevated concentrations of tissue factor, but was less effective at extending clotting time. The differential mode of action of both types of drug could be of significant therapeutic consequence (2).

A comparative investigation of the mechanisms of action of DX-9065a and argatroban (both up to 6 μM) established that only argatroban concentration-dependently accelerated the fibrinolysis of blood clots in the presence of thrombomodulin and that a differential mechanism exists between the two drugs with regard to thrombin generation, resulting in clots with alternative antifibrinolytic properties (3).

A study of the anti-factor Xa and antiprothrombinase activities of DX-9065a showed that the agent competitively inhibited the amidolytic activity of factor Xa and prothrombinase but was a noncompetitive inhibitor of prothrombin activation by the prothrombinase complex. Therapeutic heparins, on the other hand, were not effective in catalyzing the antithrombin inhibition of the prothrombinase complex during prothrombin activation (4).

DX-9065a was compared to enoxaparin in an open-label, crossover study in 6 healthy male volunteers. Treatment regimens comprised: enoxaparin 1 mg/kg s.c. plus aspirin 162 mg/day for 3 days; DX-9065a 1-mg bolus plus 0.25 mg/h for 2 h, followed by a 1-mg bolus plus 0.625 mg/h for 2 h and then a 1-mg bolus plus 1.25 mg/h for 2 h; and this schedule of DX-9065a plus aspirin pretreatment. DX-9065a alone or with aspirin significantly inhibited thrombus formation in Badimon perfusion chamber tests and had similar effects to enoxaparin on coagulation parameters (5).

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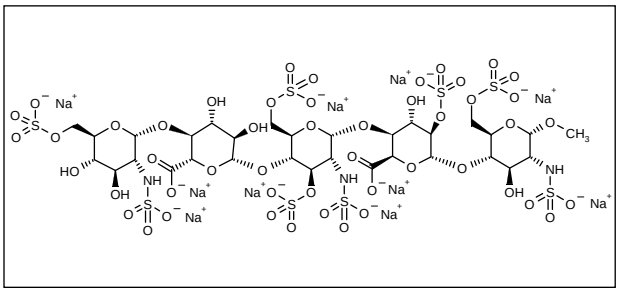
Fondaparinux Sodium



A synthetic pentasaccharide heparin analogue, fondaparinux sodium (Arixtra®) is a selective inhibitor of factor Xa via selective binding to antithrombin III (ATIII) and is representative of a new class of antithrombotic agents which aim to reduce the risk of thromboembolic events associated with major surgery.

Developed jointly by Sanofi-Synthélabo and Organon, fondaparinux was launched for the first time in the U.S. in February 2002, followed by Germany and the U.K., for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery. The recommended dose regimen is 2.5 mg once daily administered postoperatively by s.c. injection. In a pooled analysis of the clinical studies, the recommended dose regimen of fondaparinux *versus* enoxaparin was associated with a significant decrease (54%) in the rate of VTE, irrespective of the type of surgery performed. Further clinical investigations are being carried out to extend the use of fondaparinux for VTE prevention in medical and surgical high-risk situations, for the treatment of venous thrombosis and pulmonary embolism (PE), and for the treatment of patients with acute coronary syndrome (ACS). The companies subsequently received approval from the FDA for a supplemental NDA for fondaparinux for the prophylaxis of DVT, which may lead to PE, in patients undergoing hip fracture surgery, including extended prophylaxis. The usual duration of administration is 5-9 days, but an additional 24 days will be recommended in patients for whom extended prophylaxis is proposed. The approval of the new indication is based on the findings of the PENTHIFRA-PLUS study. In patients undergoing hip fracture surgery who were initially treated during the perioperative period with fondaparinux 2.5 mg s.c. once daily for 7 days, followed by a 3-week extended prophylaxis period comparing fondaparinux 2.5 mg once daily with placebo, fondaparinux was associated with a

VTE reduction of 95.9%. A file for this new indication was also submitted in Europe in December 2002 and is under review (1-5).

A phase III program comprising 2 trials is planned to investigate fondaparinux in patients with ACS. The first study, MICHELANGELO: OASIS-5 (UA/NSTEMI), will evaluate 16,000 patients with unstable angina (UA) and non-S-T segment elevation myocardial infarction (NSTEMI). The multinational, randomized, double-blind study will evaluate the efficacy and safety of fondaparinux 2.5 mg s.c. once daily *versus* enoxaparin in the acute treatment of patients with UA and NSTEMI. The primary objective is to evaluate clinical endpoints that include death, myocardial infarction or refractory ischemia within 9 days of randomization. At least 4,000 of the patients will be included in a substudy comparing early *versus* delayed revascularization procedures, and 1,600 women will be evaluated in a substudy comparing early revascularization *versus* conservative treatment. The second study, MICHELANGELO: OASIS-2 (STEMI), is a multinational study with a partial factorial design and will compare fondaparinux 2.5 mg s.c. once daily to control therapy (unfractionated heparin or placebo) and glucose-insulin-potassium infusion versus control in 10,000 patients with acute STEMI. Patients include those treated with thrombolytic regimens, primary PCI and those not eligible for reperfusion therapy. Clinical endpoints include death or myocardial infarction within 9 days of randomization. The fondaparinux regimen was chosen for these trials based on results from the phase II PENTUA (Pentasaccharide in Unstable Angina) trial in which this dose of fondaparinux was associated with a low risk of bleeding compared to enoxaparin (6).

After radiolabeled fondaparinux was incubated with postmitochondrial liver fractions from rats, rabbits, monkeys and humans, no metabolsim was detectable. In human liver microsomal preparations, no significant inhibition of oxidative metabolism of a variety of cytochrome P-450 (CYP) isoform-selective substrates (phenacetin, coumarin, tolbutamide, mephenytoin, bufuralol, chlorzoxazone, nifendipine) was observed (7).

The *in vitro* placental transfer of fondaparinux sodium (1.75 μg/ml) was evaluated and compared to that of enoxaparin sodium (1 IU/ml) using the single-pass dually perfused human cotyledon model with placentas collected from normal-term pregnancies. It was determined that fondaparinux does not cross the placental barrier (8).

The potential inhibitory effect of fondaparinux on human CYP-mediated metabolism of drugs likely to be administered concomitantly was investigated using human liver microsomal preparations in an NADPH-generating system in the presence of compounds selectively metabolized by different CYP isoforms. No significant oxidative metabolism was observed in the presence of the drug (apparent K_i values > 1000 μM), indicating that treatment with fondaparinux is unlikely to influence the pharmacokinetics of a wide range of drugs if administered concomitantly (9).

The pharmacodynamics and pharmacokinetics of two ultra-low-molecular-weight heparin-derived oligosaccharides (HDOs), C3 and RO-14, were compared with fondaparinux and a low-molecular-weight heparin (LDO). All agents were administered i.v. or s.c. to monkeys at a dose of 100 U/kg. In contrast to LDO which slightly prolonged the activated partial thromboplastin time (aPTT), no changes were observed in animals treated with the other agents i.v.; platelet counts were not affected and no increase in bleeding time or liver enzymes was observed. Fondaparinux had the longest half-life (14.2 ± 3.2 h) after i.v. administration, followed by RO-14 (12.5 ± 0.9 h), C3 (7.3 ± 0.2 h) and LDO (5.4 ± 0.3 h). The low-molecular-weight heparin had the highest relative clearance rate (13.5 ± 2 ml/h). Peak anti-Xa activity was observed following s.c. administration within 2 h for fondaparinux and C3 and within 4 h for RO-14 and LDO. Bioavailability ranged from 80% to 100%. The results suggest that the pharmacodynamics/pharmacokinetics of HDOs would be similar when compared at anti-Xa doses adjusted for potency. It was also concluded that the pharmacokinetics of heparin components are dependent on serpin affinity and molecular weight (10, 11).

The effect of recombinant activated factor VII (rFVIIa, NovoSeven; 1 μg/ml) on fondaparinux-induced thrombin generation was investigated. Fondaparinux had little effect on thrombin generation and kinetics in the presence of excess thromboplastin, but clotting triggered in the presence of physiological concentrations of thromboplastin was inhibited by fondaparinux. In the additional presence of rFVIIa, t_{max} was shortened, although fondaparinux-induced inhibition of endogenous thrombin potential was unaffected (12).

An open-label, randomized, crossover study in 24 healthy male volunteers found that coadministration of s.c. fondaparinux 10 mg and oral digoxin 0.25 mg was safe and well tolerated, and no significant pharmacokinetic interaction was observed (13).

The pharmacokinetics and pharmacodynamics of fondaparinux are not influenced by the coadministration of warfarin according to the results from a 3-way crossover, placebo-controlled trial involving 12 healthy male subjects. No differences were observed in the AUC (43 mg/l/h *vs.* 44 mg/l/h), C_{max} (645 ng/ml *vs.* 678 ng/ml), $t_{1/2}$ (13.8 h *vs.* 14.1 h) or prothrombin time (mean maximal increase of 8.2 s *vs.* 9.1 s); however, all treatments induced a small rise in aPTT (14).

Recombinant activated factor VII (rVIIa) was able to counteract the anticoagulant effect of fondaparinux in a randomized, double-blind, placebo-controlled trial in 16 healthy volunteers, suggesting that it may serve as an antidote. Study subjects received a single s.c. injection of fondaparinux 10 mg plus an i.v. bolus injection of rVIIa 90 μg/kg, fondaparinux plus an i.v. bolus injection of placebo or placebo plus rVIIa. Administration of rVIIa significantly reduced the *ex vivo* thrombin generation time, which doubled with fondaparinux treatment, and increased the *ex vivo* endogenous thrombin potential over fondaparinux treatment alone (15-18).

Table III: Clinical studies of fondaparinux sodium (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Sepsis, stroke, surgery	Open	Fondaparinux, 1 μg/ml → Antithrombin III		Variability in the response to fondaparinux in healthy volunteers and a variety of patient groups appeared to be related to levels of endogenous antithrombin III	19
Orthopedic surgery	Randomized, double-blind	Fondaparinux, 2.5 mg od sc x 19-23 d Placebo	656	Fondaparinux was well tolerated and effective as prophylaxis for venous thromboembolism in patients undergoing hip fracture surgery	20
Orthopedic surgery	Pooled/meta-analysis	Fondaparinux, 2.5 mg od sc x 11 d Enoxaparin x 11 d	7,344	The incidence of venous thromboembolism assessed during the first 11 days after major orthopedic surgery was significantly lower with fondaparinux sodium than with enoxaparin sodium, regardless of other factors such as age, gender, body mass index, the cement used in surgery, the duration of the intervention or the type of anesthesia used. Fondaparinux was more effective than enoxaparin, achieving an overall risk reduction of venous thromboembolism greater than 50% without increasing the bleeding risk in orthopedic surgery	22, 23, 27
Orthopedic surgery	Pooled/meta-analysis	Fondaparinux	2,682	Fondaparinux efficacy in preventing venous thromboembolism in patients undergoing orthopedic surgery was related to treatment duration	26
Surgery	Pooled/meta-analysis	Fondaparinux, 2.5 mg od sc x 21 ± 2 d Fondaparinux, 2.5 mg od sc x 7 ± 1 d → Placebo x 21 2 d	8,000	Fondaparinux efficacy as prophylaxis for venous thromboembolism was related to treatment duration	27

The impact of endogenous antithrombin on the efficacy of fondaparinux was assessed in plasma from healthy volunteers and patients with stroke, ACS, liver disease, sepsis or hypercoaguable state. After addition of fondaparinux 1 μg/ml, variations were seen in plasma from all of these subjects in the Heptest, the amidolytic anti-Xa test and in thrombin generation analyses. The degree of variation was reduced by 10-20%, however, with the addition of exogenous antithrombin (19). The results of this study and some that follow are summarized in Table III.

A randomized, double-blind trial compared thromboprophylaxis with once-daily fondaparinux 2.5 mg s.c. and placebo in 656 patients undergoing hip fracture surgery. Patients received fondaparinux for 6-8 days before randomization to treatment for 19-23 days. Fondaparinux was well tolerated, with a similar incidence of clinically relevant bleeding as placebo, and reduced the risk of VTE by 95.9% (20).

Data from multicenter, randomized, double-blind phase III trials of thromboprophylaxis of VTE after orthopedic surgery were analyzed to establish the efficacy of fondaparinux in over 7,000 patients undergoing major orthopedic surgery. The clinical program compared fondaparinux 2.5 mg/day s.c. postoperatively to enoxaparin 40 mg once daily preoperatively or 30 mg every 12 h postoperatively. The overall incidence of VTE to day 11 was 13.7% in patients given enoxaparin and 6.8% in those treated with fondaparinux. Fondaparinux was superior to enoxaparin regardless of a range of factors such as age, gender, body mass index and type of anesthesia used, and it was also superior to enoxaparin in meeting other composite endpoints, such as those suggested by the American College of Chest Physicians and the Committee for Proprietary Medicinal Products. The safety and the incidence of clinically relevant bleeding were similar among the groups. The efficacy of fondaparinux when administered according to the drug's labeling in the U.S. was also examined. Optimal drug safety and efficacy were seen when fondaparinux was administered according to recommendations, *i.e.*, between 6 and 8 h after surgery, excluding patients under 50 kg or with severe renal insufficiency. Regression analysis of data from these studies also revealed a significant relationship between efficacy and duration of treatment. Analysis of patients evaluable for the primary outcome of VTE up to day 11 showed a declining incidence of VTE as the treatment duration increased (21-31).

Pharmaceutical compositions comprising a 2.5-mg dose of the coagulation factor Xa inhibitor fondaparinux sodium have been claimed for the treatment of non-S-T segment elevation ACS, including unstable angina and non-Q wave acute myocardial infarction (32).

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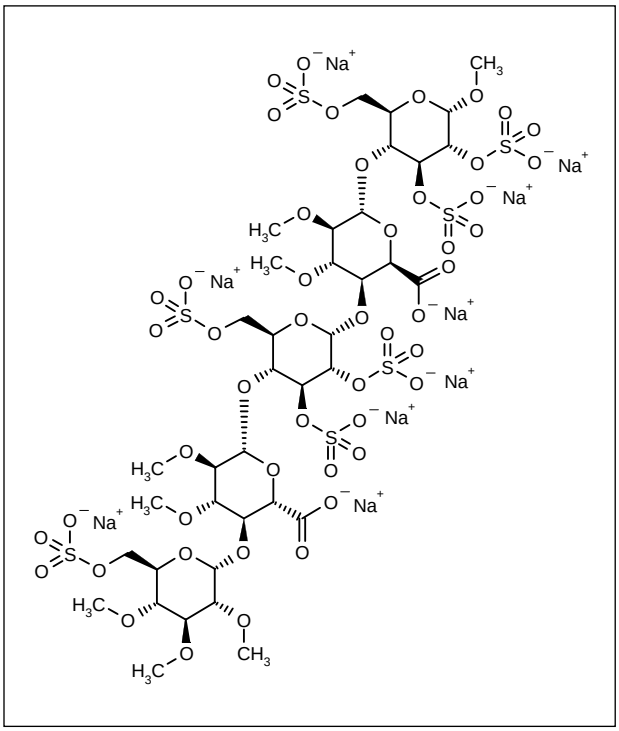
Original monograph - Drugs Fut 2002, 27(2): 122.

Idraparinux Sodium



Organon and codevelopment partner Sanofi-Synthélabo have initiated a pivotal phase III program for idraparinux sodium (SanOrg-34006, SR-34006, Org-34006), a novel once-weekly anticoagulant.

The trials will study the use of idraparinux for the long-term prevention of stroke in patients suffering from atrial fibrillation and the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). The AMADEUS study will investigate the long-term effects of idraparinux in the prevention of stroke in patients with atrial fibrillation. It is designed to demonstrate that idraparinux is at least as effective as and superior in safety to the current oral dose-adjusted anticoagulant therapy. Another set of phase III trials named Van Gogh PE, Van Gogh DVT and Van Gogh Extension (EXT) will evaluate the long-term treatment of patients with confirmed PE or DVT with idraparinux or current oral anticoagulant therapies. These studies are designed to demonstrate that idraparinux is at least as effective and superior in safety compared to current treatments. Unlike other products, idraparinux is administered once weekly rather than daily, increasing patient convenience. The results of the PERSIST study indicated that idraparinux is at least as effective as current oral anticoagulant treatment in preventing the development of new clots. In contrast to other anticoagulants, idraparinux does not require monitoring, as the phase II trial confirmed it to be very reliable and predictable in maintaining protection against recurrent venous thromboembolism over the week (1).

A phase II study randomized 659 patients to receive either warfarin or s.c. idraparinux sodium (2.5, 5.0, 7.5 or 10 mg once weekly) for 12 weeks. Both treatments induced similar changes in the thrombotic burden of the patients, although all idraparinux doses above 2.5 mg were associated with major bleeding events. A weekly dose of 2.5 mg of idraparinux was suggested to be a suitable alternative to dose-adjusted oral anti-vitamin K treatment for the prevention of DVT (2).

1. *Phase III program under way for once-weekly idraparinux*. DailyDrugNews.com (Daily Essentials) June 17, 2003.

2. Van Oers, M.H.J. et al. *A novel long-acting synthetic factor Xa inhibitor (idraparinux sodium) to replace warfarin for secondary prevention in deep vein thrombosis. A phase II evaluation*. Blood 2002, 100(11, Part 1): Abst 301.

Original monograph - Drugs Fut 2002, 27(7): 639.

Oral Heparin/SNAC

The double-blind phase III PROTECT (PROphylaxis with oral heparin/Emisphere[R] SNAC against ThromboEmbolic Complications following Total hip replacement surgery) trial evaluated Emisphere Technology's solid oral heparin formulation containing SNAC for the prevention of venous thromboembolism.

A total of 2,264 patients undergoing total hip replacement were randomized to receive oral low-dose SNAC/heparin for 30 days, oral high-dose SNAC/heparin for 30 days or s.c. low-molecular-weight heparin (LMWH; enoxaparin) for 10 days followed by oral placebo for 30 days. An ascending contrast venography conducted on days 27-30 revealed that the percentage of patients in each study group with documented DVT or PE was 31.8% (low-dose SNAC/heparin), 29.7% (high-dose SNAC/heparin) and 26.1% (LMWH). For proximal DVT or PE, the percentages were 18.6%, 13.8% and 12.7%, respectively. Poor treatment compliance was reported for the oral heparin formulations, and research aimed at finding an oral formulation with improved tolerability is currently under way. Although this trial did not meet the predetermined endpoint of superiority to injected enoxaparin, it did demonstrate the feasibility of administering heparin orally (1-3).

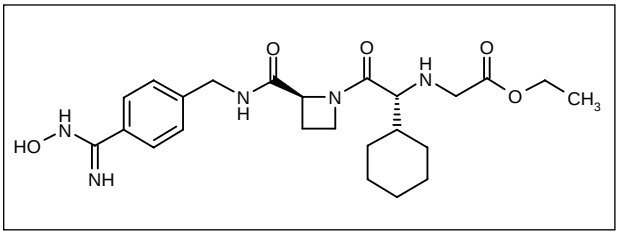
1. Hull, R.D., Kakkar, A.K., Marder, V.J., Pineo, G.F., Goldberg, M.M., Raskob, G.E. *Oral SNAC-heparin vs. enoxaparin for preventing venous thromboembolism following total hip replacement*. Blood 2002, 100(11, Part 1): Abst 558.

2. Hull, R.D., Kakkar, A.K., Marder, V.J., Pineo, G.F., Goldberg, M.M., Raskob, G.E. *Oral SNAC-heparin vs. enoxaparin for preventing venous thromboembolism following total hip replacement*. J Thromb Haemost 2003, 1(Suppl. 1): Abst P1889.

3. *Oral heparin fails to prove superiority to Lovenox in prevention of DVT*. DailyDrugNews.com (Daily Essentials) May 16, 2002.

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

Ximelagatran



Ximelagatran (H-376/95, Exanta™; AstraZeneca) is an oral direct thrombin inhibitor, the prodrug of melagatran, which is currently undergoing regulatory review in Europe for the prevention of venous thromboembolism (VTE) following major orthopedic surgery. Filings are expected later this year for the prevention of VTE in orthopedic surgery in the U.S., for the prevention of stroke in patients with atrial fibrillation in the U.S. and Europe, and for the treatment of VTE in Europe (1).

The efficacy of melagatran, unfractionated heparin, AR-C69931MX (all i.v. bolus followed by continuous infusion) and dexamethasone (i.v. bolus) on fibrin and platelet consumption and fibrin deposition was evaluated in an experimental rat model of endotoxinemia. In contrast to the partial protection provided by the other agents tested, melagatran in combination with dexamethasone completely arrested fibrinogen and platelet consumption and protected the liver and spleen from fibrin deposition (2).

The comparative antithrombotic properties and effects on bleeding of ximelagatran (1-20 μmol/kg) and warfarin (0.063-0.630 mg/kg) were evaluated in a rat vena cava thrombosis model. Animals were randomized into 10 groups receiving oral doses for 4 consecutive days. Both drugs dose-dependently lowered thrombus weight and 20 mcmol/kg ximelagatran and 0.252-0.630 mg/kg warfarin abolished thrombus formation. Although the bleeding index was considerably greater with higher doses of each, warfarin exhibited a higher index value at equieffective antithrombotic doses. Ximelagatran is therefore a favorable new oral anticoagulant for the prevention of thromboembolism (3).

A DVT treatment model was used to compare the antithrombotic effects of ximelagatran, hirudin and dalteparin in conscious rats. The mean weight of a thrombus induced by total stasis and topical ferric chloride was significantly lower at 3 h after administration of ximelagatran (2.5-20 μmol/kg p.o.) or hirudin (0.75 μmol/kg s.c.) than in control rats treated with saline or untreated reference rats. Dalteparin (200 IU/kg s.c.) was found to be less effective than the other drugs (4).

A baboon model was used to determine the effects of melagatran on the formation of thrombi. Treatment regimens consisting of an i.v. bolus injection followed by an i.v. infusion of melagatran were established: 0.05 mg/kg + 0.05 mg/kg/h, 0.15 mg/kg + 0.20 mg/kg/h, 0.3 mg/kg + 0.4 mg/kg/h and 0.6 mg/kg + 0.6 mg/kg/h. Both the rate of platelet deposition and the rate of fibrin accumulation in vascular graft segments placed within an arteriovenous shunt and exposed to 100 ml/min blood flow for 40 min decreased dose-dependently after the baboons were treated for 80 min with increasing doses of melagatran. Similar effects were found in the fibrin-rich thrombi formed distally from the grafts. The highest drug dose increased the bleeding time by 174% compared to controls, and no hemorrhages associated with melagatran were detected. The authors concluded that, compared with other thrombin inhibitors such as hirudin, melagatran reduced platelet and fibrin deposition with only a modest risk of bleeding (5).

The absorption, metabolism and excretion of ximelagatran were evaluated in rats, dogs and humans following oral and i.v. administration. Following oral administration, ximelagatran was rapidly absorbed and metabolized, with melagatran being the predominant metabolite and compound in plasma. Oral absorption was low and highly variable and the agent was primarily cleared renally. Bioavailability was 5-10% in rats, 10-50% in dogs and around 20% in humans. Following i.v. administration, plasma clearance was low, volume of distribution was small and the elimination half-life was short. It was concluded that first-pass metabolism of ximelagatran and biliary excretion of the metabolites accounted for the low bioavailability of melagatran (6).

The population pharmacokinetics of ximelagatran were evaluated in 2 studies in patients with acute DVT with or without PE. A randomized, double-blind, dose-finding study in 264 patients (24, 36, 48 or 60 mg ximelagatran b.i.d. for 12-16 days) and a pilot study in 12 patients (48 mg ximelagatran b.i.d. for 6-9 days) found that melagatran concentrations were proportional to ximelagatran dose and that the AUC values were 3.69 ± 0.16, 4.08 ± 0.42 and 3.52 ± 0.42 μmol·h/l in patients with regression, no change and progression of the thrombus, respectively. The pharmacokinetics of melagatran were

unaffected by the presence of PE in patients with DVT after oral ximelagatran (7).

An open-label, nonrandomized study in 12 obese and 12 nonobese subjects was undertaken in order to study the effect that obesity has on the pharmacokinetics and pharmacodynamics of ximelagatran (24-mg single oral dose) and its active form megalatran. The respective mean pharmacokinetic values for obese/nonobese subjects were: AUC = 1.05 ± 0.28 and 1.17 ± 0.28 μmol·h/l; C_{max} = 0.19 ± 0.07 and 0.21 ± 0.6 μmol/l; t_{max} = 2.2 ± 0.4 and 2.1 ± 0.4 h; $t_{1/2}$ = 2.9 ± 0.4 and 2.8 ± 0.3 h. No statistically significant differences were observed between groups, suggesting that no dose alterations are required in obese patients receiving this drug (8).

Three studies were undertaken to evaluate the pharmacokinetics of melagatran in patients with nonvalvular atrial fibrillation treated for prevention of stroke and systemic embolism. A multicenter, double-blind, randomized, parallel-group, dose-guiding study (20, 40 or 60 mg ximelagatran b.i.d.) with warfarin in 153 patients, an open-label follow-up of the first study (36 mg b.i.d. ximalagatran) with warfarin in 49 patients and a 5-day study (36 mg ximelagatran b.i.d.) in 12 patients with a low risk of stroke found that the $t_{1/2}$ of melagatran was 5 h and a linear relationship was observed between drug clearance and renal function. Results for pharmacokinetics were as expected, exhibited low variability and were not affected by dose, treatment time or group (9-11).

The potential effects of alcohol consumption on the pharmacokinetics and pharmacodynamics of ximelagatran were assessed in a randomized, crossover clinical trial. Twenty-six healthy subjects aged 20-40 years received a single oral dose of 36 mg of ximelagatran with or without ethanol at a dose of 0.6 or 0.5 mg/kg for men and women, respectively. Ethanol had no significant effect on the peak plasma concentrations of ximelagatran or on the aPTT of the patients. The drug was also well tolerated both alone and combined with ethanol and induced no relevant changes in the laboratory variables or vital signs of the subjects (12). The results of this study and some that follow are summarized in Table IV.

In a randomized, open-label study, 120 healthy male volunteers were given ximelagatran 15, 30 or 60 mg or recombinant hirudin i.v. or enoxaparin s.c. at doses known to be clinically effective in ACS. All treatments produced rapid and significant inhibition of thrombin generation and platelet activation, and inhibition of thrombin generation was comparable for recombinant hirudin, enoxaparin and ximelagatran 60 mg (13).

In a multicenter, randomized, double-blind trial, 680 patients who had undergone total knee arthroplasty were treated with oral ximelagatran 24 mg b.i.d. or warfarin for 7-12 days. Ximelagatran was at least as effective as warfarin in preventing VTE, which occurred in 19.2% and 25.7% of patients, respectively. Bleeding parameters were also similar between treatment groups (14).

A clinical trial compared hemostasis parameters in 9 patients with DVT who had received either placebo or ximelagatran (24 mg p.o. b.i.d.) for 18 months after an initial 6-month treatment with warfarin. The analysis of blood samples taken 13-17 months after the beginning of the treatment revealed that ximelagatran significantly decreased both the overall hemostatic potential and the overall coagulation potential and increased the clot lysis time of the patients compared with placebo. All of these parameters returned to control levels when measured at 6 months after cessation of therapy. Patients treated with ximelagatran also reported a reduction in fibrinolysis that might be related with an upregulation of the thrombin-activatable fibrinolysis inhibitor (15).

The THRIVE Treatment Study was a double-blind, randomized clinical trial that compared the effects of ximelagatran and a combination of enoxaparin and warfarin in the prevention of DVT. A total of 2,491 patients suffering from acute DVT with or without PE received ximelagatran (36 mg b.i.d. for 6 months) or enoxaparin (1 mg/kg s.c. b.i.d. for at least 5 days) followed by warfarin (target International Normalized Ratio of 2.0-3.0 for 6 months). At 6 months, patients receiving the ximelagatran regimen showed a similar incidence of recurrent VTE (2.1% *vs*. 2.0%), and a reduced all-cause mortality rate (2.3% *vs*. 3.4%) and incidence of major bleeding (1.3% *vs*. 2.2%) compared to those treated with the combination (16).

In the double-blind, randomized THRIVE III study, 1,233 patients with VTE who had received standard anticoagulation therapy for 6 months were randomized to receive placebo or ximelagatran (24 mg p.o. b.i.d.) for 18 months. The drug was more effective than placebo in reducing the percentage of patients who reported recurrent VTE during the study period (2.0% *vs*. 11.6%) and the rate of composite endpoint all-cause mortality and recurrent VTE. The overall incidence of hemorrhage was slightly higher with ximelagatran (21.9% *vs*. 18.1%), but few patients treated with the drug experienced major hemorrhage and none were fatal or intracerebral (17).

The effects of time and dose on the prevention of DVT and PE after total hip or knee replacement were assessed by a meta-analysis that pooled the results from 3 double-blind, randomized clinical trials: the METHRO II, METHRO III (Melagatran for Thrombin Inhibition in Surgery) and EXPRESS (Expanded Prophylaxis Evaluation Surgery Study) studies. A total of 6,312 patients were randomized to receive either a regimen of s.c. melagatran and oral ximelagatran, or the low-molecular-weight heparins dalteparin and enoxaparin. After 8-11 days of treatment, a preoperative dose of 2-3 mg of melagatran was found to be associated with a lower incidence of DVT or PE than the low-molecular-weight heparins or no preoperative administration of melagatran. An increased efficacy was also directly related to a higher rate of bleeding events. The authors concluded that a regimen consisting of a preoperative dose of 2 mg of melagatran s.c. followed by 3 mg of melagatran s.c. and 24 mg of ximelagatran p.o. b.i.d. was well tolerated and achieved a good balance between prevention of DVT/PE and surgical bleeding (18).

Table IV: Clinical trials of ximelagatran/melagatran (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, open, crossover	Ximelagatran, 36 mg po Ximelagatran, 36 mg po sd + Ethanol, 0.6 [0.5 for women] g/kg po	26	The coadministration of ximelagatran with ethanol had no effect on the drug's safety profile or on the laboratory variables or vital signs of healthy volunteers	12
Healthy volunteers	Randomized, open	Ximelagatran, 15 mg po (n=20) Ximelagatran, 30 mg po (n=20) Ximelagatran, 60 mg po (n=20) Deshirudin, 0.4 mg/kg iv bolus → 0.15 mg/kg/h infusion over 2 h + 0.075 mg/kg/h infusion over 2 h (n=20) Enoxaparin, 100 U/kg sc (n=20) Water (n=20)	120	Ximelagatran, deshirudin and enoxaparin produced rapid and significant inhibition of thrombin generation and platelet activation	13
Prophylaxis deep venous thrombosis	Randomized, double-blind, multicenter	Ximelagatran, 24 mg po bid x 7-12 d (start after surgery) Warfarin po od (adjusted to INR 2.5) x 7-12 d (start before surgery)	675	Ximelagatran 24 mg orally was safe and effective as a prophylactic agent for venous thromboembolism in arthroplasty and did not require routine coagulation monitoring	14
Thrombo-embolism	Randomized, double-blind	Warfarin x 6 mo → Ximelagatran, 24 mg po bid x 18 mo (n=4) Warfarin x 6 mo → Placebo (n=5)	9	Compared with placebo, ximelagatran administered for 18 months increased clot lysis time and decreased both overall hemostatic potential and overall coagulation potential in patients with deep venous thromboembolism	15
Thrombo-embolism	Randomized, double-blind, multicenter	Ximelagatran, 36 mg po bid x 6 mo (n=1241) Enoxaparin, 1 mg/kg sc bid x 5 [min] d → Warfarin [target international normalized ratio 2.0-3.0] x 6 mo (n=1250)	2,491	After 6 months of treatment, ximelagatran was as effective as enoxaparin plus warfarin in preventing recurrent venous thromboembolism and was associated with a lower mortality and a lower incidence of major bleeding	16
Thrombo-embolism	Randomized, double-blind, multicenter	Ximelagatran, 24 mg po bid x 18 mo (n=612) Placebo (n=611)	1,233	A fixed oral dose of ximelagatran 24 mg twice daily was effective and well tolerated in the prevention of recurrent venous thromboembolism	17
Prophylaxis deep venous thrombosis	Randomized, double-blind, pooled/meta-analysis	Melagatran, 0 mg sc [preoperative] → Melagatran, 3 mg sc → Ximelagatran, 24 mg po bid x 8-11 d Melagatran, 2 mg sc [preoperative] → Melagatran, 3 mg sc → Ximelagatran, 24 mg po bid x 8-11 d Melagatran, 3 mg sc [preoperative] → Melagatran, 3 mg sc → Ximelagatran, 24 mg po bid x 8-11 d Dalteparin or Enoxaparin	6,312	The administration of a preoperative s.c. dose of melagatran 2 mg followed by s.c. melagatran and oral ximelagatran significantly decreased the incidence of deep vein thrombosis and/or pulmonary embolism in patients undergoing total hip or knee replacement and was associated with a slight increase in the incidence of surgical bleeding	18
Thrombo-embolism	Open	Ximelagatran, 36 mg po bid x 6 mo	18	Twice-daily administration of ximelagatran 36 mg increased both prothrombin time and activated partial thromboplastin time in patients who suffered an episode of acute deep vein thrombosis	20
Prophylaxis deep venous thrombosis	Randomized, double-blind, multicenter	Ximelagatran, 24 mg po bid x 7-12 d (n=757) Ximelagatran, 36 mg po bid x 7-12 d (n=769) Warfarin, target INR 2.5 po x 7-12 d (n=759)	2,285	Ximelagatran 36 mg twice daily was more effective than warfarin in preventing venous thromboembolism after total knee replacement. No significant differences were found between warfarin and ximelagatran in the incidence of bleeding events after 7-12 days of treatment	21

Continuation

Table IV (Cont.): Clinical trials of ximelagatran/melagatran (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Atrial fibrillation	Randomized, multicenter	Ximelagatran, 20 mg bid x 12 wk Ximelagatran, 40 mg bid x 12 wk Ximelagatran, 60 mg bid x 12 wk Warfarin [INR = 2-3]	254	Ximelagatran was well tolerated in patients with nonvalvular atrial fibrillation	22

Results from the EXPRESS trial of ximelagatran/melagatran, presented at the 17th International Congress on Thrombosis in Bologna late last year, showed that is was more effective than enoxaparin in reducing the risk of major VTE in major orthopedic surgery. EXPRESS was a double-blind, randomized phase III trial in Europe and South Africa conducted in 2,800 patients comparing the efficacy and safety of ximelagatran/melagatran with prophylactic treatment with s.c. enoxaparin (40 mg once daily) for the prevention of VTE following major hip and knee replacement surgery. Patients received 2 mg s.c. melagatran immediately before surgery, followed by 3 mg s.c. in the evening after surgery and 24 mg oral ximelagatran as a fixed dose. The results showed a significant 63% relative risk reduction (2.3% *vs.* 6.3%) in major VTE, proximal DVT and PE, in patients treated with ximelagatran/melagatran compared with enoxaparin. A relative risk reduction in major VTE of 67% (1.8% *vs.* 5.5%) was seen in total hip replacement surgery and a 60% relative risk reduction (3.3% *vs.* 8.2%) in total knee replacement surgery. Additionally, there was a 24% (20.3% *vs.* 26.6%) reduction in the risk of total VTE (proximal and distal DVT and PE) following prophylactic treatment with ximelagatran/melagatran compared with enoxaparin. A small increase in surgery-related bleeding was observed on ximelagatran/melagatran compared with enoxaparin, but there was no difference in clinically important bleeding events (19).

A dose of 36 mg of ximelagatran administered twice daily increased both the prothrombin time and the aPTT in 18 patients with acute DVT. Its therapeutic effects were similar to those found with heparin or recombinant hirudin. No evidence of accumulation was found for the drug after 6 months of therapy (20).

A multicenter, double-blind phase III clinical trial randomized 2,301 patients undergoing total knee replacement to receive fixed oral doses of ximelagatran (24 or 36 mg b.i.d.) or warfarin (target International Normalized Ratio of 2.5) for 7-12 days, starting during the evening of the day of surgery (warfarin) or the morning after surgery (ximelagatran). At day 12 after surgery, the total incidence of VTE was 27.6% with warfarin, 24.9% with ximelagatran 24 mg and 20.3% with ximelagatran 36 mg; the frequency of proximal VTE and death was also lower with ximelagatran (2.5% and 2.7% for the 24- and 36-mg doses, respectively) than with warfarin (4.1%). No significant differences were found in the incidence of bleeding. The overall results confirmed that an oral dose of 36 mg of ximelagatran administered twice daily was safe and effective in preventing VTE after total knee replacement (21).

Ximelagatran 20, 40 or 60 mg b.i.d. or warfarin was given to 254 patients with nonvalvular atrial fibrillation and at least 1 additional risk factor for stroke in a 12-week, randomized trial. Ximelagatran was well tolerated, and no major bleeds were associated with its use. In the ximelagatran groups, 1 ischemic stroke and 1 transient ischemic attack (TIA) occurred; 2 TIAs occurred in the warfarin group (22).

Headline results from AstraZeneca's recently completed SPORTIF III (Stroke Prevention ORal Thrombin Inhibitor in atrial Fibrillation) trial comparing ximelagatran with warfarin are reported to be encouraging. The data support the positive benefit/risk profile for ximelagatran for the prevention of stroke in atrial fibrillation (23).

Subcutaneous melagatran was evaluated as prophylaxis for VTE after total hip or total knee replacement in 2 clinical studies. Doses between 1.5 and 6 mg b.i.d. were administered in a poloxamer depot formulation to 66 patients in one study and 104 patients received doses of 2-4 mg b.i.d. in saline or as a depot formulation in cyclodextrin in the other study. Treatment began just before surgery and was continued for 8-11 days. Doses up to 4.5 mg b.i.d. were well tolerated and the incidence of VTE was low (24).

A pharmaceutical composition comprising the thrombin inhibitor melagatran in combination with the antiinflammatory synthetic glucocorticoid dexamethasone, or pharmaceutically acceptable derivatives of either, in an admixture formulation with a pharmaceutically acceptable adjuvant, diluent or carrier has been claimed for the treatment of conditions in which inflammation is a distinguishing symptom, and/or thrombin inhibition is required, and/or in which coagulation is induced at least in part via inflammation. Targeted conditions include the systemic secondary thrombohemorrhagic disorder disseminated intravascular coagulation (DIC) (25).

Oral pharmaceutical compositions comprising the thrombin inhibitor ximelagatran in combination with sodium dodecyl sulfate (SDS) and a polymer such as hydroxypropyl methylcellulose (HPMC), hydroxyethyl cellulose (HEC) or polyoxyethylene oxide (PEO) have been claimed for the prevention and/or treatment of cardiovascular disorders such as thromboembolism (26).

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