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(71) Applicant (for all designated States except DE, US):
BOEHRINGER INGELHEIM INTERNATIONAL GMBH [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(71) Applicant (for DE only): **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **CLEMENS, Andreas** [DE/DE]; Nibelungenstr. 6, 65187 Wiesbaden (DE).
CRONIN, Lisa [CA/CA]; 5180 South Service Road, Burlington, Ontario L7L 5H4 (CA).

(74) Agents: **HAMMANN, Heinz** et al.; Binger Str. 173, 55216 Ingelheim am Rhein (DE).

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(54) Title: NEW PAEDIATRIC INDICATIONS FOR DIRECT THROMBIN INHIBITORS

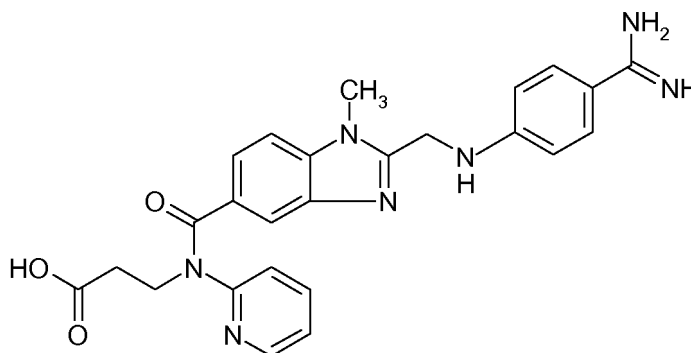
(57) Abstract: The invention relates to new paediatric indications for direct thrombin inhibitors such as dabigatran etexilate.

New paediatric indications for direct thrombin inhibitors

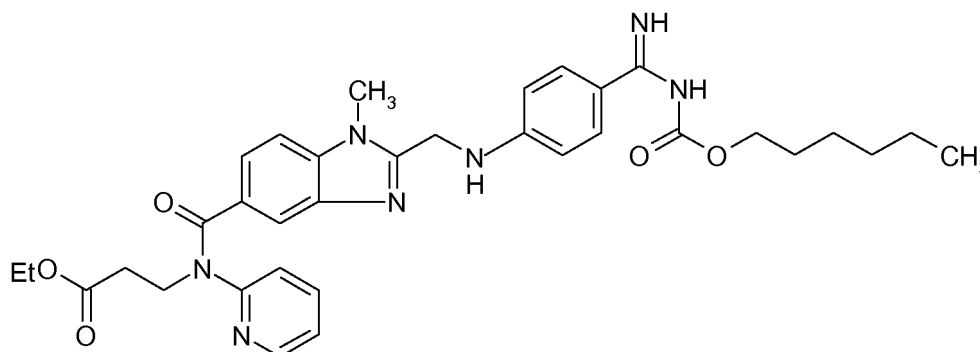
The present invention relates to novel indications for direct thrombin inhibitors (DTI), processes for preparing pharmaceutical compositions for treating said diseases and methods of treating them.

Direct thrombin inhibitors according to the invention include

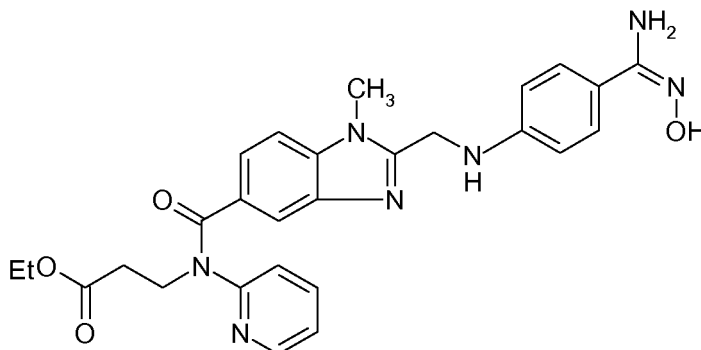
- 10 (1) 1-methyl-2-(4-amidinophenylaminomethyl)-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-hydroxycarbonyl-ethyl)-amide known as dabigatran having the structure



- 15 (2) ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate known as dabigatran etexilate having the following structure



- (3) 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide having the structure



5

- (4) melagatran (inogatran),
 (5) ximelagatran,
 (6) hirudin,
 (7) hirolog and
 10 (8) argatroban,

optionally in the form of tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates, hydrates or prodrugs thereof.

15

Preferred direct thrombin inhibitors are dabigatran, dabigatran etexilate and 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide, and the tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates, hydrates and prodrugs thereof.

20

More preferred are dabigatran and dabigatran etexilate, and the tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates, hydrates and prodrugs thereof.

25

Most preferred is dabigatran etexilate, and the tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts,

solvates, hydrates and prodrugs thereof, particularly its acid addition salt with methanesulfonic acid.

All active components should be used in effective amounts.

5

The active compounds (1) to (3) are disclosed in the prior art, e.g. in WO 98/37075 and WO 04/014894. The acid addition salt of dabigatran etexilate with methanesulfonic acid is described in WO 03/074056. Additional salts of dabigatran etexilate are mentioned in the experimental part. Specific polymorphs and a hemihydrate of acid addition salt of dabigatran etexilate with methanesulfonic acid is described in WO 2005/028468. Examples for pharmaceutical composition containing dabigatran etexilate are disclosed in WO 03/074056, WO 2005/018615 and WO 2005/023249.

15 Prodrugs of the drugs mentioned above are such derivatives containing one or more groups capable of being cleaved in vivo, particularly a group which can be converted in-vivo into a carboxy group or/and a group capable of being cleaved in vivo from an imino or amino group. Compounds containing two groups capable of being cleaved in vivo are so-called double prodrugs. Groups which can be converted in-vivo into a carboxy group and groups capable of being cleaved in vivo from an imino or amino group are disclosed e.g. in WO 98/37075, being herewith incorporated by reference, as well as in other WO publications cited hereinbefore in connection with specific antithrombotics.

25 It is understood that the direct thrombin inhibitor according to the invention may be used in a form selected from tautomers, optical isomers, enantiomers, racemates, diastereomers, pharmacologically acceptable acid addition salts, solvates or hydrates, as far as such forms exist, depending on the individual compound. If multiple enantiomers exist, the use in form of a substantially pure enantiomer is preferred.

30

Pharmacological acceptable acid addition salts of the direct thrombin inhibitors listed above comprise salts selected from the group consisting of the hydro-

chloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydro-
methanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate,
hydrocitrate, hydrofumarate, hydrotartrate, hydrolactate, hydrooxalate, hydro-
succinate, hydrobenzoate and hydro-p-toluolsulphonate, preferably hydro-
5 chloride, hydrobromide, hydrosulphate, hydrophosphate, hydromaleate, hydro-
fumarate and hydromethansulphonate. Some of the direct thrombin inhibitors
may add more than one equivalent acid, e.g. two equivalents. The salts of
hydrochloric acid, methanesulfonic acid, maleic acid, benzoic acid and acetic
acid are especially preferred.

10

A preferred embodiment are the salts of dabigatran etexilate with hydrochloric
acid, maleic acid, tartaric acid, salicylic acid, citric acid, methanesulfonic acid and
malonic acid, the enantiomers, mixtures and hydrates thereof. Particularly pre-
ferred are tartaric acid, salicylic acid, methanesulfonic acid and citric acid as well
15 as the enantiomers, mixtures and hydrates thereof. The most preferred salt of is
the methanesulfonic acid addition salt of dabigatran etexilate.

The following terms are used synonymously:

- salt with hydrochloric acid - hydrochloride
- 20 salt with maleic acid - maleate
- salt with tartaric acid - tartrate
- salt with salicylic acid - salicylate
- salt with citric acid - citrate
- salt with malonic acid – malonate
- 25 salt with methanesulfonic acid - methanesulfonate

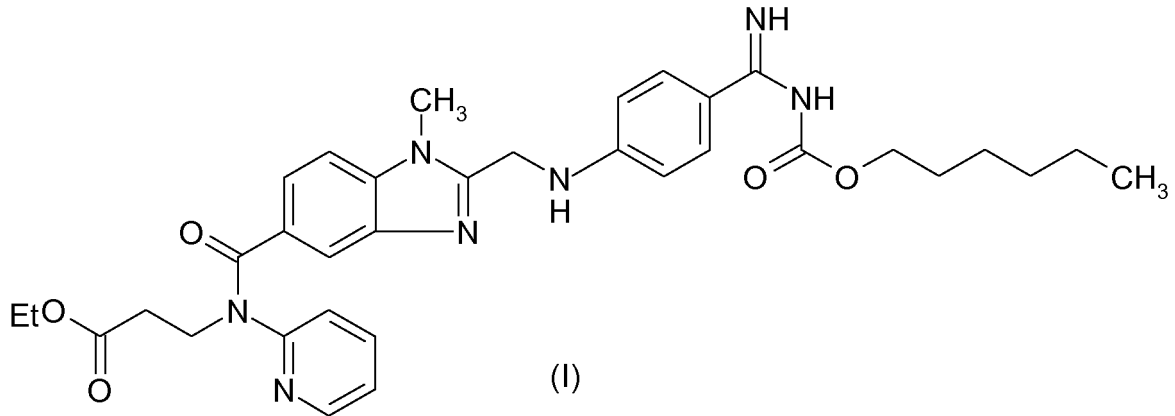
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Any reference to a direct thrombin inhibitor within the scope of the present
invention should be understood as a reference to any specific direct thrombin
inhibitor selected from compounds (1) to (8) mentioned hereinbefore.

A preferred embodiment of the invention relates to new indications of the active
substance ethyl 3-[(2-[[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-
methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate,

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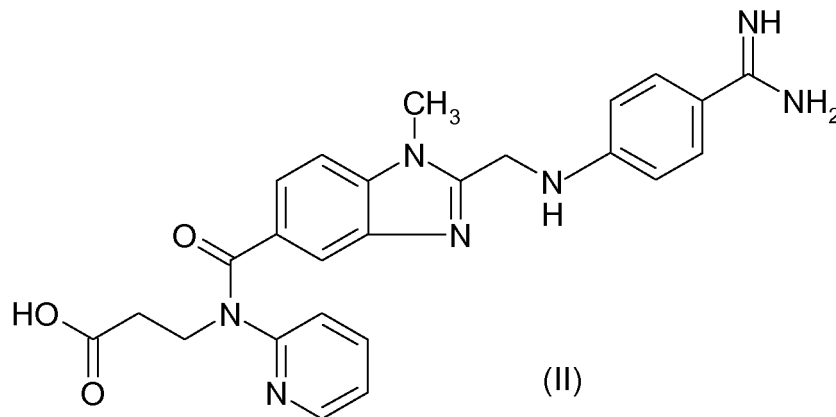
the salts, the enantiomers, the mixtures and the hydrates thereof. This active substance with the chemical formula



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is already known from WO 98/37075, wherein compounds with a thrombin-inhibiting and thrombin time-prolonging activity are disclosed, under the name 1-methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino)phenyl]-amino-methyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl ethyl)-amide. The

10 compound of formula I is a double prodrug of the compound



i.e. the compound of formula I is first converted into the actual effective compound, namely the compound of formula II, in the body. The main type of indication for the compound of chemical formula I is the post-operative prophylaxis of deep vein thrombosis and the prevention of strokes.

15

Surprisingly, the direct thrombin inhibitors like e.g. dabigatran etexilate cannot only be used effectively for the post-operative prophylaxis of deep vein throm-

basis and the prevention of strokes, but are also suitable for the prevention and/or treatment of children.

In particular the invention relates to the use of a compound, optionally in the form of tautomers, racemates, enantiomers, diastereomers, pharmacologically acceptable acid addition salts, solvates, hydrates or prodrugs thereof, selected from the group consisting of dabigatran, dabigatran etexilate, 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide, melagatran (inogatran), ximelagatran, hirudin, hirolog and argatroban for preparing a medicament for the treatment and/or prophylaxis of a disease selected from among thrombosis and/or venous thromboembolic events (VTE) in children, preferably VTE selected from among primary VTE prevention, secondary VTE prevention and VTE treatment in children.

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of stroke in children, preferably for the treatment of non haemorrhagic stroke in children or for stroke prevention in children selected from among primary and secondary stroke prevention in children with atrial fibrillation and primary and secondary stroke prevention in children at elevated risk for stroke (children after transitoric ischemic attack (TIA) or stroke and post myocard infarction or acute coronary syndrome in children, children with very low ejection fraction of the heart).

In yet another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of myocardial infarction (sometimes also named acute coronary syndrome [ACS]) in children,

preferably ACS resp. myocardial infarction in children
with/after stent implantation,
with percutaneous coronary intervention (PCI) without stent
5 implantation
and without PCI in children.

The treatment and/or prophylaxis of myocardial infarction resp. ACS may either
begin immediately after the event (acute treatment) or a certain time after the
10 event (e.g. after myocardial infarction, post-MI) (chronic therapy, secondary
prevention).

In yet another embodiment the invention relates to the use of the compounds
mentioned hereinbefore for preparing a medicament for the treatment and/or
15 prophylaxis of myocardial infarction in children, in particular myocardial infarction
in children with arterio coronary venous bypass (ACVB) and also in children after
thrombolysis.

In another embodiment the invention relates to the use of the compounds
20 mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of thrombosis or thromboembolic events in children with an off pump
coronary artery by pass grafting surgery.

In another embodiment the invention relates to the use of the compounds
25 mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of graft thrombosis in children, in particular graft thrombosis in ACVB
children and also in children after thrombolysis.

In another embodiment the invention relates to the use of the compounds
30 mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of stroke in children, particularly for the prevention of stroke in
children with atrial fibrillation.

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of post-operative prophylaxis of deep vein thrombosis (DVT) in children.

5

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of thrombosis or thromboembolic events in children, in particular in off pump coronary artery bypass and/or grafting surgery.

10

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of stent thrombosis in children, in particular stent thrombosis in PCI patients and also in patients after thrombolysis

15

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of elevated cardiovascular risk in children, preferably elevated cardiovascular risk in children under treatment with antihypertensive and/or lipid lowering drugs, in children with elevated inflammatory status, in children with elevated coagulant parameters (e.g. PAI 1) or in children with diabetes mellitus.

20

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of congenital heart disease in children, in particular open foramen ovale, congenital heart failure, congenital disposition of the vessels and vessel anomalies (e.g. aortic isthmus stenosis) in children.

25

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of diseases selected from among disorders in children, e.g. due to artificial heart valves, arrhythmia, heart failure, hypertrophic obstructive cardiomyopathy (HOCM) and diabetes mellitus.

30

- In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of peripheral arterial disease (PAD) in children, in particular of
5 peripheral arterial disease
in children suffering from diabetes mellitus,
in children with or without implanted stent(-s) in the peripheral vessel(-s)
and in children who underwent peripheral bypass surgery.
- 10 In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of a disease selected from among brain micro vessel disease and pulmonary infarction in children.
- 15 In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the prevention and/or treatment of shunt thrombosis, catheter thrombosis (including central venous line [CVL]) and thromboembolic events in children, in particular in children on dialysis with shunt or without shunt and in the dialysis machine.
- 20 In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for the treatment and/or prophylaxis of pulmonary embolism (PE) in children, in particular of PE in children with higher risk for PE (e.g. congenital coagulopathy, children after multiple pulmonary embolisms) and
25 in children with deep venous thromboembolism (DVT) and/or any other kind of VTE.
- In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or
30 prophylaxis of thrombosis, venous thromboembolic events (VTE), pulmonary embolism (PE) and deep venous thromboembolism (DVT) (anticoagulant therapy) in medical care children (immobilized children), in particular
in children immobilized after any kind of surgery,

10

in children immobilized after any kind of accident or trauma,
in immobilized children with additional risk factors for VTE,
in children with cancer, particularly in children with acute
lymphoblastic leukaemia (ALL),
5 in children with heart failure,
in children with multiple sclerosis (MS) or
in children with another diagnosis which results in immobiliza-
tion of the child.

10 In another embodiment the invention relates to the use of the compounds
mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of of the diseases mentioned in this application occurring in pregnant
girls, in particular stroke, heart failure (high risk gravidas), congenital hyper-
coagulation disease and haemolysis in pregnant girls, as well as for the
15 treatment and/or prophylaxis of elevated liver enzymes and low platelets
(HELLP) syndrome (in pregnant girls).

In another embodiment the invention relates to the use of the compounds
mentioned hereinbefore for preparing a medicament for the treatment and/or
20 prophylaxis of acute or chronic arterial thromboembolism (for example due to
cardiac catheterisation, central venous line (CVL) etc.) in children.

Herein, prophylaxis includes application prior to surgery resp. catheterisation as
well as during the surgery resp. catheterisation.

25

In another embodiment the invention relates to the use of the compounds
mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of congenital heart disease in children, in particular postoperative
congenital heart disease in children and VTE in children.

30

In another embodiment the invention relates to the use of the compounds
mentioned hereinbefore for preparing a medicament for the treatment and/or
prophylaxis of venous thromboembolism and/or VTE in children with cancer (e.g.

acute lymphoblastic leukaemia (ALL)), particularly in children under chemotherapy involving Asparaginase.

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or

prophylaxis of a disease selected from the group consisting of:
neurodegenerative disease,
brain micro vessel disease,
diseases which are mediated via PAR 1 to PAR 4 receptors
and oxidative stress induced by thrombin in children.

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of

Haematological diseases,
heparin induced thrombocytopenia (HIT),
disseminated intravascular coagulation (DIC) in children.

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of a disease selected from among

thrombosis in children,
thrombosis and/or venous thromboembolic events in polychemotherapy (particularly in polychemotherapy involving Asparaginase) in children suffering from cancer, particularly in children suffering from leukaemia such as acute lymphoblastic leukaemia (ALL).

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of central vein thrombosis (CVT) in children.

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of HIV encephalitis in children suffering from human immunodeficiency virus (HIV).

5

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of rheumatoid disorders in children, in particular rheumatoid arthritis and systemic lupus erythematoses (SLE) in children.

10

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of Tinnitus Aurium in children.

15

In another preferred embodiment the invention is related to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis of kidney disease in children, in particular proteinuria (urinary albumin excretion) in patients with chronic kidney disease and proteinuria (urinary albumin excretion) in patients with Diabetes and albuminuria.

20

The thrombin inhibitors listed above are useful for the prevention and/or treatment of events provoked by the above-mentioned diseases (like VTE, PE), optimize the blood flow to organs or regions, and/or are suitable for direct treatment of the diseases.

25

A preferred embodiment is the use of the direct thrombin inhibitors according to the invention for the preparation of a medicament for treating or preventing VTE associated with any one of the diseases mentioned above resp. below.

30

The term "patient" as used in this application is to be understood as referring to children. Within the meaning of the instant invention children are patients with an

age below 18 years, preferably, below 16 years, more preferably below 14 years, yet more preferably below 12 years. In particular children may be patients with an age in the range of 1 to 10 years.

- 5 A preferred group of patients are children up to 5 years old; another preferred group of patients are children between 6 and 10 years; yet another preferred group of patients are children between 11 and 16 years.

Preferred indications are:

- 10 treatment of non-haemorrhagic stroke in children,
primary and secondary stroke prevention in children with very low
ejection fraction of the heart;
acute stroke in children,
treatment and/or prophylaxis of myocardial infarction resp. acute
15 coronary syndrome (ACS) in children, preferably ACS resp. myocardial
infarction in children
with/after stent implantation,
with percutaneous coronary intervention (PCI) without stent
implantation,
20 without PCI in children;
treatment and/or prophylaxis of thrombosis, venous thromboembolic
events (VTE), pulmonary embolism (PE) and deep venous thrombo-
embolism (DVT) in medical care children (immobilized children), in
particular
25 in children immobilized after any kind of surgery,
in children immobilized after any kind of accident or trauma,
in children with additional risk factors for VTE,
in children with cancer,
in children with heart failure,
30 in children with multiple sclerosis (MS) or
in children with another diagnosis which results in immobiliza-
tion of the child;

treatment and/or prophylaxis of elevated cardiovascular risk in children, preferably elevated cardiovascular risk in

children under treatment with antihypertensive and/or lipid lowering drugs,

5 children with elevated inflammatory status,

children with elevated coagulant parameters (e.g. PAI 1) or in children with diabetes mellitus;

treatment and/or prophylaxis of congenital heart disease in children, in particular

10 open foramen ovale,

congenital heart failure,

congenital disposition of the vessels and

vessel anomalies in children;

treatment and/or prophylaxis of cardiovascular disorders in children

15 due to

artificial heart valves in children,

arrhythmia in children,

heart failure in children,

hypertrophic obstructive cardiomyopathy (HOCM) in children

20 or

diabetes mellitus in children;

treatment and/or prophylaxis of peripheral arterial disease (PAD) in children, in particular PAD

in children with diabetes mellitus,

25 in children with or without implanted stent(-s) in the peripheral vessel(-s) and

in children who underwent peripheral bypass surgery;

treatment and/or prophylaxis of brain micro vessel disease in children;

treatment and/or prophylaxis of pulmonary infarction in children;

30 treatment and/or prophylaxis of shunt thrombosis in children,

particularly in children on dialysis,

treatment and/or prophylaxis of catheter thrombosis in children,

particularly in children on dialysis,

treatment and/or prophylaxis of thromboembolic events in the dialysis machine;

treatment and/or prophylaxis of pulmonary embolism (PE) in children, in particular of PE in children with higher risk for PE (e.g. congenital coagulopathy, children after multiple pulmonary embolisms); treatment and/or prophylaxis of stroke in pregnant girls, of heart failure in pregnant girls (high risk gravidas), of

congenital hypercoagulation disease in pregnant girls, of haemolysis in pregnant girls and of elevated liver enzymes and low platelets (HELLP) syndrome in pregnant girls;

treatment and/or prophylaxis of thrombosis or thromboembolic events in children with an off pump coronary artery bypass grafting;

1) CNS-field

- a. neurodegenerative disease (e.g. Alzheimer disease) in children
- b. brain micro vessel disease in children
- c. diseases which are mediated via PAR 1 to PAR 4 receptors in children
- d. oxidative stress induced by thrombin in children

2) Haematologic disease

- a. Heparin induced thrombocytopenia in children
- b. children with elevated coagulant parameters (e.g. PAI 1)
- c. Disseminated intravascular coagulation (DIC) in children

3) Cancer

- a. Primary and secondary prevention and/or treatment of cancer in children
- b. Prevention of thrombosis in polychemotherapy in children, particularly in polychemotherapy including Asparaginase,
- c. Prevention of thrombosis in children
- d. Treatment of thrombosis in children
- e. Mortality reduction as mono-therapy and in combination with anti-cancer agents in children

4) Ophthalmology

- a. Central vein thrombosis (CVT) in children

- 5) Human Immunodeficiency Virus (HIV) patients
 - a. HIV encephalitis in children
- 6) Rheumatoid disorders in children
 - a. Rheumatoid arthritis in children
 - 5 b. Systemic Lupus erythematosus (SLE) in children
- 7) Children with transplantation
- 8) Children with implants
 - a. shunt prosthesis in children on dialysis
 - b. prosthesis of the vessel (Aorta etc.) in children
- 10 9) Children with Tinnitus Aurium
- 10) Children with kidney disease
 - a. Proteinuria (urinary albumin excretion) in patients with chronic kidney disease
 - b. Proteinuria (urinary albumin excretion) in patients with Diabetes and
 - 15 albuminuria.

In another embodiment the invention relates to the use of the compounds mentioned hereinbefore for preparing a medicament for the treatment and/or prophylaxis in children of one or several of the diseases mentioned hereinbefore, wherein the disease is associated with VTE.

The direct thrombin inhibitor, optionally used in form of its pharmaceutically acceptable acid addition salts, may be incorporated into the conventional pharmaceutical preparation in solid, liquid or spray form. The composition may, for example, be presented in a form suitable for oral, topical, lingual, rectal, parenteral administration or for nasal inhalation: preferred forms includes for example, capsules, tablets, coated tablets, ampoules, suppositories and nasal spray.

The active ingredient may be incorporated in excipients or carriers conventionally used in pharmaceutical compositions such as, for example, talc, arabic gum, lactose, gelatine, magnesium stearate, corn starch, aqueous or non aqueous vehicles, polyvinyl pyrrolidone, semisynthetic glycerides of fatty acids, benz-

alconium chloride, sodium phosphate, EDTA, polysorbate 80. The compositions are advantageously formulated in dosage units, each dosage unit being adapted to supply a single dose of the active ingredient. The dosis range applicable per day is between 0.1 mg to 600 mg, preferably between 50 mg to 300 mg/day.

5 Each dosage unit may conveniently contain from 0.1 mg to 200 mg, preferably from 50 mg to 150 mg.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

15

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

20

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. of a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

30

Solutions for injection are prepared in the usual way, e.g. of. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal

salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

5 Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

10 Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

The Examples which follow illustrate the present invention without restricting its scope:

- 5 The starting material dabigatran etexilate (ethyl 3-[(2-[[4-(amino-hexyloxy-carbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate) may for example be prepared as described in International Application WO 98/37075, Example 113.

10 Example 1

Hydrochloride of ethyl 3-[(2-[[4-(amino-hexyloxy-carbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate

- 15 125 mg (1.59 mmol) of acetyl chloride were added to 5 ml ethanol with stirring. The solution thus obtained was then added dropwise at ambient temperature to a solution of 1.0 g (1.59 mmol) of ethyl 3-[(2-[[4-(amino-hexyloxy-carbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate and stirred for a further two hours. The mixture was then
- 20 evaporated down completely, the residue was first of all triturated after the addition of approx. 5 ml ethyl acetate and suction filtered, then stirred overnight in approx. 10 ml acetone, suction filtered, washed with a little acetone and diethyl ether and then dried at 60°C *in vacuo*.

Yield: 86% of theory

- 25 Melting point: 135 °C

Example 2

- Citric acid salt of ethyl 3-[(2-[[4-(amino-hexyloxy-carbonylimino-methyl)-phenyl-amino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate
-

210 mg (1.0 mmol) of citric acid hydrate, dissolved in 10 ml ethyl acetate, were added dropwise at ambient temperature with stirring to a solution of 628 mg (1.0 mmol) of ethyl 3-[(2-[[4-(amino-hexyloxy-carbonylimino-methyl)-phenylamino]-

methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in 45 ml ethyl acetate. A yellow precipitate formed. The mixture was stirred overnight, the product was then suction filtered, washed with a little ethyl acetate and diethyl ether and dried at approx. 50°C *in vacuo*.

5 Yield: 83% of theory

Melting point: approx. 170 °C (with decomposition)

Example 3

10 Tartaric acid salt of ethyl 3-[(2-[[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate

150 mg (1.0 mmol) of L(+)-tartaric acid, dissolved in 5 ml absolute ethanol, were added dropwise at ambient temperature with stirring to a solution of 628 mg (1.0

15 mmol) of ethyl 3-[(2-[[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in 50 ml ethyl acetate. A fine precipitate was formed. The suspension was stirred for a further two hours, then the product was suction filtered, washed with a little cold ethyl acetate and diethyl ether and dried *in vacuo* at approx. 50°C.

20 Yield: 72% of theory

Melting point: approx. 160 °C (with decomposition)

Example 4

25 Malonic acid salt of ethyl 3-[(2-[[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate

104 mg (1.0 mmol) of malonic acid, dissolved in 10 ml ethyl acetate, were added dropwise at ambient temperature, with stirring, to a solution of 628 mg (1.0

30 mmol) of ethyl 3-[(2-[[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl]-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in 50 ml ethyl acetate. After approx. one hour a fine precipitate formed. The suspension was stirred for a further three hours, the product was then suction

filtered, washed with a little cold ethyl acetate and diethyl ether and dried *in vacuo* at approx. 50°C.

Yield: 79% of theory

Melting point: 100 °C

5

Example 5

Maleic acid salt of ethyl 3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-
10 amino]-propionate

116 mg (1.0 mmol) of maleic acid, dissolved in 10 ml ethyl acetate, were added dropwise, with stirring, at ambient temperature, to a solution of 628 mg (1.0 mmol) of ethyl 3-[(2-{[4-(amino-hexyloxycarbonylimino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate in
15 50 ml ethyl acetate. A precipitate formed. The suspension was stirred for a further three hours, then the product was suction filtered, washed with a little cold ethyl acetate and diethyl ether and dried *in vacuo* at approx. 50°C.

Yield: 93% of theory

Melting point: 120 °C

20

Example 6

Ethyl-3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate salicylate

25 A solution of 1.38 g (10.0 mmol) of salicylic acid in 20 ml acetone was added dropwise with stirring at 35 - 40°C to a solution of 6.28 g (10.0 mmol) of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1*H*-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base (prepared as described in WO 98/37075), in 45 ml acetone. After a few minutes the product
30 began to crystallise out and it was diluted with 65 ml acetone. Within 30 minutes the mixture was cooled to ambient temperature, then the precipitate was suction filtered, washed with approx. 40 ml acetone and dried at 40°C in the circulating air dryer.

Yield: 94% of theory

Melting point: 155 °C

5 Example 7

Dry ampoule containing 75 mg active substance per 10 ml

Composition:

10	active substance	75.0 mg
	mannitol	50.0 mg
	water for injections	ad 10.0 ml

Preparation:

- 15 Active substance and mannitol are dissolved in water. After packaging the solution is freeze-dried. To produce the solution ready for use for injections, the product is dissolved in water.

20 Example 8

Dry ampoule containing 35 mg of active substance per 2 ml

Composition:

25

	Active substance	35.0 mg
	Mannitol	100.0 mg
	water for injections	ad 2.0 ml

30 Preparation:

- Active substance and mannitol are dissolved in water. After packaging, the solution is freeze-dried.

To produce the solution ready for use for injections, the product is dissolved in water.

Example 9

5

Tablet containing 50 mg of active substance

Composition:

10	(1) Active substance	50.0 mg
	(2) Lactose	98.0 mg
	(3) Maize starch	50.0 mg
	(4) Polyvinylpyrrolidone	15.0 mg
	(5) Magnesium stearate	<u>2.0 mg</u>
15		215.0 mg

Preparation:

(1), (2) and (3) are mixed together and granulated with an aqueous solution of
20 (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 9 mm.

Example 10

Tablet containing 350 mg of active substance

5

Composition:

(1) Active substance	350.0 mg
(2) Lactose	136.0 mg
10 (3) Maize starch	80.0 mg
(4) Polyvinylpyrrolidone	30.0 mg
(5) Magnesium stearate	<u>4.0 mg</u>
	600.0 mg

Preparation:

- 15 (1), (2) and (3) are mixed together and granulated with an aqueous solution of (4). (5) is added to the dried granulated material. From this mixture tablets are pressed, biplanar, faceted on both sides and with a dividing notch on one side. Diameter of the tablets: 12 mm.

20

Example 11

Capsules containing 50 mg of active substance

25

Composition:

(1) Active substance	50.0 mg
(2) Dried maize starch	58.0 mg
(3) Powdered lactose	50.0 mg
(4) Magnesium stearate	<u>2.0 mg</u>
30	160.0 mg

Preparation:

(1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

5 This powder mixture is packed into size 3 hard gelatine capsules in a capsule filling machine.

Example 12

Capsules containing 350 mg of active substance

10

Composition:

(1) Active substance	350.0 mg
(2) Dried maize starch	46.0 mg
15 (3) Powdered lactose	30.0 mg
(4) Magnesium stearate	<u>4.0 mg</u>
	430.0 mg

Preparation:

20 (1) is triturated with (3). This trituration is added to the mixture of (2) and (4) with vigorous mixing.

This powder mixture is packed into size 0 hard gelatine capsules in a capsule filling machine.

Example 13

Suppositories containing 100 mg of active substance

5

1 suppository contains:

	Active substance	100.0 mg
	Polyethyleneglycol (M.W. 1500)	600.0 mg
	Polyethyleneglycol (M.W. 6000)	460.0 mg
10	Polyethylenesorbitan monostearate	<u>840.0 mg</u>
		2,000.0 mg

Example 14

	Percentage composition				per capsule [mg]	per capsule [mg]
	Core material	Separating layer	Active substance layer	Total		
Tartaric acid	61.3	-	-	61.3	176.7	353.4
Gum arabic	3.1	2.8		5.9	17.0	34.0
Talc	-	5.6	3.2	8.8	25.4	50.7
Hydroxyhydroxypropyl-cellulose	-	-	4.0	4.0	11.5	23.1
Active substance (based on the base)	-	-	20.0	20.0	50.0	100.0
Total				100.0	288.3	576.5

15

Example 15

	Percentage composition				per capsule [mg]	per capsule [mg]
	Core material	Separating layer	Active substance layer	Total		
Tartaric acid	38.5	-	-	38.5	55.5	166.5
Gum arabic	1.9	1.7		3.6	5.2	15.6
Talc	-	3.5	6.4	9.9	14.3	42.8
Hydroxyhydroxypropyl-cellulose	-	-	8.0	8.0	11.5	34.6
Active substance (based on the base)	-	-	40.0	40.0	50.0	150.0
Total				100.0	144.2	432.5

- 5 The preparation and the structure of the pellets according to Examples 14 and 15 is described in detail in WO 03/074056.

Patent Claims

1. Use of a compound, optionally in the form of tautomers, racemates, enan-
5 tiomers, diastereomers, pharmacologically acceptable acid addition salts,
solvates, hydrates or prodrugs thereof, selected from the group consisting of
dabigatran, dabigatran etexilate, 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylamino-
methyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-
amide, melagatran (inogatran), ximelagatran, hirudin, hirolog and argatroban for
10 preparing a medicament for the treatment and/or prophylaxis in children of a
disease selected from the group consisting of:

non-haemorrhagic stroke,
primary and secondary stroke prevention in children with very low
15 ejection fraction of the heart;
acute stroke, acute coronary syndrome (ACS);
myocardial infarction;
elevated cardiovascular risk;
congenital heart disease;
20 artificial heart valves;
arrhythmia;
heart failure;
hypertrophic obstructive cardiomyopathy (HOCM);
diabetes mellitus;
25 peripheral arterial disease (PAD);
brain micro vessel disease;
pulmonary infarction;
off pump coronary artery bypass grafting;
shunt thrombosis;
30 catheter thrombosis;
thromboembolic events in the dialysis machine;
pulmonary embolism (PE);
medical care children (immobilized children);

- cancer;
stroke in pregnant girls,
heart failure in pregnant girls (high risk gravidas),
congenital hypercoagulation disease in pregnant girls,
5 hemolysis, elevated liver enzymes and low platelets (HELLP)
syndrome in pregnant girls;
neurodegenerative disease,
brain micro vessel disease,
diseases which are mediated via PAR 1 to PAR 4 receptors,
10 oxidative stress induced by thrombin,
haematology,
heparin induced thrombocytopenia,
thrombosis in poly chemotherapy,
central vein thrombosis (CVT),
15 HIV encephalitis,
rheumatoid disorders,
tinnitus Aurium and
kidney disease.
- 20 2. The use according to claim 1 wherein the disease is associated with VTE.
3. The use according to one of claims 1 or 2 characterized in that the compound
is selected from the group consisting of dabigatran, dabigatran etexilate and 1-
methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-benzimidazol-5-yl-
25 carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonyl-ethyl)-amide.
4. The use according to one of claims 1 to 3 characterized in that the compound
is selected from the group consisting of dabigatran and dabigatran etexilate or a
pharmacologically acceptable acid addition salt thereof.
- 30 5. The use according to one of claims 1 to 4 characterized in that the compound
is dabigatran etexilate or a pharmacologically acceptable acid addition salt
thereof.

6. The use according to one of claims 1 to 5 characterized in that the compound is the acid addition salt of dabigatran etexilate with methanesulfonic acid.

5 7. Use according to one of claims 1 to 6 characterized in that the compound is applied in a dosis range between 0.1 mg to 600 mg per day.

8. A method for the treatment and/or prophylaxis in children of a disease selected from the group consisting of:

10

non-haemorrhagic stroke,
primary and secondary stroke prevention in children with very low
ejection fraction of the heart;

acute stroke;

15

acute coronary syndrome (ACS);

myocardial infarction;

elevated cardiovascular risk;

congenital heart disease;

artificial heart valves;

20

arrhythmia;

heart failure;

hypertrophic obstructive cardiomyopathy (HOCM);

diabetes mellitus;

peripheral arterial disease (PAD);

25

brain micro vessel disease;

pulmonary infarction;

shunt thrombosis;

catheter thrombosis;

thromboembolic events in the dialysis machine;

30

off pump coronary artery bypass grafting;

pulmonary embolism (PE);

medical care children (immobilized children);

cancer;

stroke in pregnant girls,
heart failure in pregnant girls (high risk gravidas),
congenital hypercoagulation disease in pregnant girls,
hemolysis, elevated liver enzymes and low platelets (HELLP)
5 syndrome in pregnant girls;
neurodegenerative disease,
brain micro vessel disease,
diseases which are mediated via PAR 1 to PAR 4 receptors,
oxidative stress induced by thrombin,
10 haematology,
heparin induced thrombocytopenia,
thrombosis in poly chemotherapy,
central vein thrombosis (CVT),
HIV encephalitis,
15 rheumatoid disorders,
tinnitus Aurium and
kidney disease,

said method comprising the step of administering to a child in need thereof a
20 therapeutically effective amount of a compound, optionally in the form of tauto-
mers, racemates, enantiomers, diastereomers, pharmacologically acceptable
acid addition salts, solvates, hydrates or prodrugs thereof, selected from the
group consisting of dabigatran, dabigatran etexilate, 1-methyl-2-[4-(*N*-hydroxy-
amidino)-phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-
25 ethoxycarbonylethyl)-amide, melagatran (inogatran), ximelagatran, hirudin,
hirolog and argatroban.

9. The method according to claim 8 wherein the disease is associated with VTE.

30 10. The method according to one of claims 8 or 9 characterized in that the
compound is selected from the group consisting of dabigatran, dabigatran
etexilate and 1-methyl-2-[4-(*N*-hydroxyamidino)-phenylaminomethyl]-
benzimidazol-5-yl-carboxylic acid-(*N*-2-pyridyl-*N*-2-ethoxycarbonylethyl)-amide.

11. The method according to one of claims 8 to 10 characterized in that the compound is selected from the group consisting of dabigatran and dabigatran etexilate or a pharmacologically acceptable acid addition salt thereof.

5

12. The method according to one of claims 8 to 11 characterized in that the compound is dabigatran etexilate or a pharmacologically acceptable acid addition salt thereof.

10 13. The method according to one of claims 8 to 12 characterized in that the compound is the acid addition salt of dabigatran etexilate with methanesulfonic acid.

14. Method according to one of claims 8 to 13 characterized in that the compound is applied in a dosis range between 0.1 mg to 600 mg per day.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/057258

A. CLASSIFICATION OF SUBJECT MATTER INV. A61K45/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CETTA F ET AL: "Pediatric and congenital heart disease" CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS, [Online] vol. 61, no. 1, 18 December 2003 (2003-12-18), pages 147-149, XP002449276 Wiley InterScience Retrieved from the Internet: URL:http://www3.interscience.wiley.com/cgi-bin/abstract/106576708/ABSTRACT> [retrieved on 2007-09-04]	1-5, 7-12,14
Y	abstract ----- -/--	1-5, 7-12,14
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C.		
<input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents :		
A document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *&* document member of the same patent family	
Date of the actual completion of the international search <p align="center">5 September 2007</p>	Date of mailing of the international search report <p align="center">13/11/2007</p>	
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <p align="center">Bendl, Ernst</p>	

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2007/057258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HURSTING M ET AL: "Argatroban anticoagulation in pediatric patients: a literature analysis" JOURNAL OF PEDIATRIC HEMATOLOGY / ONCOLOGY, [Online] vol. 28, no. 1, January 2006 (2006-01), XP002449277 Wolter Kluwer Health Retrieved from the Internet: URL:http://www.jpho-online.com/pt/re/jpho/abstract.00043426-200601000-00002.htm;jsessionid=Gd0KTFv3DQ5JghzKQR06ZmHD676tyqFyTxzGlsyyq36QlswtDBXZ-9333867511811956288091-1> [retrieved on 2007-09-04] abstract</p> <p>-----</p>	1-5, 7-12,14
X	<p>KUHLE S ET AL: "Comparison of the anticoagulant effects of melagatran and LMWH in an acquired antithrombin deficiency with ALL treated with L-asparaginase: an ex vivo study" JOURNAL OF THROMBOSIS AND HAEMOSTASIS, [Online] vol. 3, no. Suppl.1, 12 August 2005 (2005-08-12), XP002449278 Blackwell Synergy Retrieved from the Internet: URL:http://www.blackwellpublishing.com/isth2005/abstract.asp?id=45731> [retrieved on 2007-09-04] abstract</p> <p>-----</p>	1-5, 7-12,14
X	<p>"Boehringer Ingelheim launches industry's largest thromboembolic disease clinical trial program to date" PRESS RELEASE, [Online] 24 January 2006 (2006-01-24), pages 1-2, XP002449279 Boehringer Ingelheim Retrieved from the Internet: URL:http://us.boehringer-ingelheim.com/newroom/2006/01-24-06_dabigatran.html> [retrieved on 2007-09-04]</p>	1-5, 7-12,14
Y	<p>page 1, paragraph 1 - paragraph 2</p> <p>-----</p> <p style="text-align: center;">-/--</p>	1-5, 7-12,14

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2007/057258

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>KENNETH A BAUER: "New Anticoagulants: Anti IIa vs Anti Xa-Is One Better?" JOURNAL OF THROMBOSIS AND THROMBOLYSIS, KLUWER ACADEMIC PUBLISHERS, BO, vol. 21, no. 1, 1 February 2006 (2006-02-01), pages 67-72, XP019216045 ISSN: 1573-742X abstract page 68, left-hand column</p>	1-5, 7-12,14
Y	<p>WO 2004/112645 A (BROWN WARD M [US]) 29 December 2004 (2004-12-29) page 5, paragraph 16 page 7, paragraph 21 - paragraph 22</p>	1-5, 7-12,14
Y	<p>US 2006/034847 A1 (YUN ANTHONY J [US] ET AL) 16 February 2006 (2006-02-16) page 3 paragraph [0027] paragraph [0033] paragraph [0063]</p>	1-5, 7-12,14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2007/057258

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 8-14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

see annex

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claim:

Invention 1 (Claims 1 (part), 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of non-haemorrhagic stroke

2. claim:

Invention 2 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the primary
and secondary stroke prevention in children with very low
ejection fraction of the heart

3. claim:

Invention 3 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of acute stroke, acute coronary
syndrome

4. claim:

Invention 4 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of myocardial infarction

5. claim:

Invention 5 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of elevated cardiovascular risk

6. claim: ---

Invention 6 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of congenital heart disease

7. claim:

Invention 7 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of artificial heart valves

8. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 8 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of arrhtmia

9. claim:

Invention 9 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of heart failure

10. claim:

Invention 10 (Claims 1 (part, 2-4, 7, 8 (part), 9-11, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of hypertrophic obstructive
cardiomyopathy

11. claim:

Invention 11 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of diabetes mellitus

12. claim:

Invention 12 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of peripheral arterial disease

13. claim:

Invention 13 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of brain micro vessel disease

14. claim:

Invention 14 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of pulmonary infarction

15. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 15 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of off pump coronary artery bypass
grafting

16. claim:

Invention 16 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of shunt thrombosis

17. claim:

Invention 17 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of catheter thrombosis

18. claim:

Invention 18 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of thrombolytic events in the
dialysis machine

19. claim:

Invention 19 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of pulmonary embolism

20. claim:

Invention 20 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of medical care children

21. claim:

Invention 21 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of cancer

22. claim:

Invention 22 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of stroke in pregnant girls

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

23. claim:

Invention 23 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of heart failure in pregnant girls

24. claim:

Invention 24 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of congenital hypercoagulation
disease in pregnant girls

25. claim:

Invention 25 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of hemolysis, elevated liver enzymes
and low platelets syndrom in pregnant girls

26. claim:

Invention 26 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of neurodegenerative disease

27. claim:

Invention 27 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of brain micro vessel disease

28. claim:

Invention 28 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of diseases which are mediated via
PAR 1 to PAR4 receptors

29. claim:

Invention 29 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of oxidative stress induced by
thrombin

30. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 30 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of heparin induced thrombocytopenia

31. claim:

Invention 31 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of thrombosis in poly chemotherapy

32. claim:

Invention 32 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of central vein thrombosis

33. claim:

Invention 33 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of HIV encephalitis

34. claim:

Invention 34 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of rheumatoid disorders

35. claim:

Invention 35 (Claims 1 (part, 2-5, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of tinnitus aurium

36. claim:

Invention 36 (Claims 1 (part, 2-4, 7, 8 (part), 9-12, 14):
Use / method applying dabigatran (etexilate) for the
treatment / prevention of kidney disease

37. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 37 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 1-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazol-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of non-haemorrhagic stroke

38. claim:

Invention 38 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 1-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazol-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the primary and secondary stroke prevention in children with very low ejection fraction of the heart

39. claim:

Invention 39 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazol-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of acute stroke, acute coronary syndrome

40. claim:

Invention 40 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazol-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of myocardial infarction

41. claim:

Invention 41 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazol-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of elevated cardiovascular risk

42. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 42 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of congenital heart disease

43. claim:

Invention 43 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of artificial heart valves

44. claim:

Invention 44 ((Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of arrhythmia

45. claim:

Invention 45 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of heart failure

46. claim:

Invention 46 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of hypertrophic obstructive cardiomyopathy

47. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 47 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of diabetes mellitus

48. claim:

Invention 48 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of peripheral arterial disease

49. claim:

Invention 49 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of brain micro vessel disease

50. claim:

Invention 50 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of pulmonary infarction

51. claim:

Invention 51 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
 Use / method applying
 -methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of off pump coronary artery bypass grafting

52. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 52 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of shunt thrombosis

53. claim:

Invention 53 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of catheter thrombosis

54. claim:

Invention 54 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of thrombolytic events in the dialysis machine

55. claim:

Invention 55 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of pulmonary embolism

56. claim:

Invention 56 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of medical care children

57. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 57 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of cancer

58. claim:

Invention 58 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of stroke in pregnant girls

59. claim:

Invention 59 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of heart failure in pregnant girls

60. claim:

Invention 60 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of congenital hypercoagulation disease in pregnant girls

61. claim:

Invention 61 ((Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of hemolysis, elevated liver enzymes and low platelets syndrom in pregnant girls

62. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 62 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of neurodegenerative disease

63. claim:

Invention 63 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of brain micro vessel disease

64. claim:

Invention 64 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of diseases which are mediated via PAR 1 to PAR4 receptors

65. claim:

Invention 65 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of oxidative stress induced by thrombin

66. claim:

Invention 66 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the treatment / prevention of heparin induced thrombocytopenia

67. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 67 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of thrombosis in poly chemotherapy

68. claim:

Invention 68 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of central vein thrombosis

69. claim:

Invention 69 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of HIV encephalitis

70. claim:

Invention 70 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of rheumatoid disorders

71. claim:

Invention 71 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic acid-(N-2-pyridyl-N-2-ethoxycarbonyl-ethyl)-amide for the treatment / prevention of tinnitus aurium

72. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 72 (Claims 1 (part), 2-3, 7, 8 (part), 9-10, 14):
Use / method applying
-methyl-2-[4-(N-hydroxyamidino)-phenylamino-methyl]benzimidazole-5-yl-carboxylic
acid-(N-2-pyridyl-N-2-ethoxycarbonylethyl)-amide for the
treatment / prevention of kidney disease

73. claim:

Invention 73 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of non-haemorrhagic stroke

74. claim:

Invention 74 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the primary and secondary
stroke prevention in children with very low ejection
fraction of the heart

75. claim:

Invention 75 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of acute stroke, acute coronary syndrome

76. claim:

Invention 76 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of myocardial infarction

77. claim:

Invention 77 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of elevated cardiovascular risk

78. claim:

Invention 78 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of congenital heart disease

79. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 79 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of artificial heart valves

80. claim:

Invention 80 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of arrhtmia

81. claim:

Invention 81 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of heart failure

82. claim:

Invention 82 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of hypertrophic obstructive cardiomyopathy

83. claim:

Invention 83 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of diabetes mellitus

84. claim:

Invention 84 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of peripheral arterial disease

85. claim:

Invention 85 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of brain micro vessel disease

86. claim:

Invention 86 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of pulmonary infarction

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

87. claim:

Invention 87 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of off pump coronary artery bypass grafting

88. claim:

Invention 88 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of shunt thrombosis

89. claim:

Invention 89 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of catheter thrombosis

90. claim:

Invention 90 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of thrombolytic events in the dialysis machine

91. claim:

Invention 91 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of pulmonary embolism

92. claim:

Invention 92 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of medical care children

93. claim:

Invention 93 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of cancer

94. claim:

Invention 94 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of stroke in pregnant girls

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

95. claim:

Invention 95 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of heart failure in pregnant girls

96. claim:

Invention 96 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of congenital hypercoagulation disease in
pregnant girls

97. claim:

Invention 97 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of hemolysis, elevated liver enzymes and low
platelets syndrom in pregnant girls

98. claim:

Invention 98 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of neurodegenerative disease

99. claim:

Invention 99 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use /
method applying (xi)melagatran for the treatment /
prevention of brain micro vessel disease

100. claim:

Invention 100 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying (xi)melagatran for the treatment /
prevention of diseases which are mediated via PAR 1 to PAR4
receptors

101. claim:

Invention 101 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying (xi)melagatran for the treatment /
prevention of oxidative stress induced by thrombin

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

102. claim:

Invention 102 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of heparin induced thrombocytopenia

103. claim:

Invention 103 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of thrombosis in poly chemotherapy

104. claim:

Invention 104 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of central vein thrombosis

105. claim:

Invention 105 (Claims 1 (part), 2, 7, 8 (part), 9, 14)): Use / method applying (xi)melagatran for the treatment / prevention of HIV encephalitis

106. claim:

Invention 106 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of rheumatoid disorders

107. claim:

Invention 107 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of tinnitus aurium

108. claim:

Invention 108 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying (xi)melagatran for the treatment / prevention of kidney disease

109. claim:

Invention 109 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of non-haemorrhagic stroke

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

110. claim:

Invention 110 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the primary and secondary stroke prevention in children with very low ejection fraction of the heart

111. claim:

Invention 111 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of acute stroke, acute coronary syndrome

112. claim:

Invention 112 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of myocardial infarction

113. claim:

Invention 113 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of elevated cardiovascular risk

114. claim:

Invention 114 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of congenital heart disease

115. claim:

Invention 115 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of artificial heart valves

116. claim:

Invention 116 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of arrhythmia

117. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 117 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of heart failure

118. claim:

Invention 118 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of hypertrophic obstructive cardiomyopathy

119. claim:

Invention 119 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of diabetes mellitus

120. claim:

Invention 120 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of peripheral arterial disease

121. claim:

Invention 121 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of brain micro vessel disease

122. claim:

Invention 122 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of pulmonary infarction

123. claim:

Invention 123 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of off pump coronary artery bypass grafting

124. claim:

Invention 124 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of shunt thrombosis

125. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 125 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of catheter thrombosis

126. claim:

Invention 126 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of thrombolytic events in the dialysis machine

127. claim:

Invention 127 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of pulmonary embolism

128. claim:

Invention 128 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of medical care children

129. claim:

Invention 129 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of cancer

130. claim:

Invention 130 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of stroke in pregnant girls

131. claim:

Invention 131 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of heart failure in pregnant girls

132. claim:

Invention 132 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of congenital hypercoagulation disease in pregnant girls

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

133. claim:

Invention 133 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of hemolysis, elevated liver enzymes and low platelets syndrom in pregnant girls

134. claim:

Invention 134 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of neurodegenerative disease

135. claim:

Invention 135 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of brain micro vessel disease

136. claim:

Invention 136 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of diseases which are mediated via PAR 1 to PAR4 receptors

137. claim:

Invention 137 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of oxidative stress induced by thrombin

138. claim:

Invention 138 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of heparin induced thrombocytopenia

139. claim:

Invention 139 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirudin for the treatment / prevention of thrombosis in poly chemotherapy

140. claim:

Invention 140 (Claims 1 (part), 2-5, 7, 8 (part), 9-12, 14): Use / method applying hirudin for the treatment / prevention of central vein thrombosis

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

141. claim:

Invention 141 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirudin for the treatment / prevention of
HIV encephalitis

142. claim:

Invention 142 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirudin for the treatment / prevention of
rheumatoid disorders

143. claim:

Invention 143 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirudin for the treatment / prevention of
tinnitus aurium

144. claim:

Invention 144 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirudin for the treatment / prevention of
kidney disease

145. claim:

Invention 145 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirolog for the treatment / prevention of
non-haemorrhagic stroke

146. claim:

Invention 146 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirolog for the primary and secondary
stroke prevention in children with very low ejection
fraction of the heart

147. claim:

Invention 147 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use
/ method applying hirolog for the treatment / prevention of
acute stroke, acute coronary syndrome

148. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 148 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of myocardial infarction

149. claim:

Invention 149 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of elevated cardiovascular risk

150. claim:

Invention 150 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of congenital heart disease

151. claim:

Invention 151 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of artificial heart valves

152. claim:

Invention 152 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of arrhtmia

153. claim:

Invention 153 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of heart failure

154. claim:

Invention 154 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of hypertrophic obstructive cardiomyopathy

155. claim:

Invention 155 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of diabetes mellitus

156. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 156 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of peripheral arterial disease

157. claim:

Invention 157 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of brain micro vessel disease

158. claim:

Invention 158 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of pulmonary infarction

159. claim:

Invention 159 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of off pump coronary artery bypass grafting

160. claim:

Invention 160 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of shunt thrombosis

161. claim:

Invention 161 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of catheter thrombosis

162. claim:

Invention 162 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of thrombolytic events in the dialysis machine

163. claim:

Invention 163 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of pulmonary embolism

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

164. claim:

Invention 164 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of medical care children

165. claim:

Invention 165 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of cancer

166. claim:

Invention 166 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of stroke in pregnant girls

167. claim:

Invention 167 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of heart failure in pregnant girls

168. claim:

Invention 168 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of congenital hypercoagulation disease in pregnant girls

169. claim:

Invention 169 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of hemolysis, elevated liver enzymes and low platetelts syndrom in pregnant girls

170. claim:

Invention 170 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of neurodegenerative disease

171. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 171 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of brain micro vessel disease

172. claim:

Invention 172 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method hirolog for the treatment / prevention of diseases which are mediated via PAR 1 to PAR4 receptors

173. claim:

Invention 173 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method hirolog for the treatment / prevention of oxidative stress induced by thrombin

174. claim:

Invention 174 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of heparin induced thrombocytopenia

175. claim:

Invention 175 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of thrombosis in poly chemotherapy

176. claim:

Invention 176 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of central vein thrombosis

177. claim:

Invention 177 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of HIV encephalitis

178. claim:

Invention 178 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of rheumatoid disorders

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

179. claim:

Invention 179 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of tinnitus aurium

180. claim:

Invention 180 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying hirolog for the treatment / prevention of kidney disease

181. claim:

Invention 181 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of non-haemorrhagic stroke

182. claim:

Invention 182 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the primary and secondary stroke prevention in children with very low ejection fraction of the heart

183. claim:

Invention 183 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of acute stroke, acute coronary syndrome

184. claim:

Invention 184 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of myocardial infarction

185. claim:

Invention 185 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of elevated cardiovascular risk

186. claim:

Invention 186 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of congenital heart disease

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

187. claim:

Invention 187 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of artificial heart valves

188. claim:

Invention 188 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of arrhtmia

189. claim:

Invention 189 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of heart failure

190. claim:

Invention 190 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of hypertrophic obstructive cardiomyopathy

191. claim:

Invention 191 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of diabetes mellitus

192. claim:

Invention 192 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of peripheral arterial disease

193. claim:

Invention 193 (Claims 1 (part), 2, 7, 8 (part), 9, 14)): Use / method applying argatroban for the treatment / prevention of brain micro vessel disease

194. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 194 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of pulmonary infarction

195. claim:

Invention 195 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of off pump coronary artery bypass grafting

196. claim:

Invention 196 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of shunt thrombosis

197. claim:

Invention 197 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of catheter thrombosis

198. claim:

Invention 198 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of thrombolytic events in the dialysis machine

199. claim:

Invention 199 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of pulmonary embolism

200. claim:

Invention 200 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of medical care children

201. claim:

Invention 201 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of cancer

202. claim:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Invention 202 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of stroke in pregnant girls

203. claim:

Invention 203 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of heart failure in pregnant girls

204. claim:

Invention 204 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of congenital hypercoagulation disease in pregnant girls

205. claim:

Invention 205 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of hemolysis, elevated liver enzymes and low platelets syndrom in pregnant girls

206. claim:

Invention 206 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying d argatroban for the treatment / prevention of neurodegenerative disease

207. claim:

Invention 207 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of brain micro vessel disease

208. claim:

Invention 208 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of diseases which are mediated via PAR 1 to PAR4 receptors

209. claim:

Invention 209 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of oxidative stress induced by thrombin

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

210. claim:

Invention 210 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of heparin induced thrombocytopenia

211. claim:

Invention 211 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of thrombosis in poly chemotherapy

212. claim:

Invention 212 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of central vein thrombosis

213. claim:

Invention 213 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of HIV encephalitis

214. claim:

Invention 214 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of rheumatoid disorders

215. claim:

Invention 215 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of tinnitus aurium

216. claim:

Invention 216 (Claims 1 (part), 2, 7, 8 (part), 9, 14): Use / method applying argatroban for the treatment / prevention of kidney disease

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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