(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 200 118 B1

(12) EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention of the grant of the patent:
16.01.2008 Bulletin 2008/03

(21) Application number: 00928047.0

(22) Date of filing: 19.04.2000

(51) Int Cl.:
A61K 38/55 (2006.01) *A61K 38/06* (2006.01)
A61P 9/14 (2006.01)

(86) International application number:
PCT/SE2000/000756

(87) International publication number:
WO 2000/064470 (02.11.2000 Gazette 2000/44)

(54) A PHARMACEUTICAL FORMULATION COMPRISING MEGALATRAN AND ITS PRODRUG

PHARMAZEUTISCHE FORMULIERUNG ENTHALTEND MEGALATRAN UND DESSEN PRO-PHARMAKA

FORMULATION PHARMACEUTIQUE COMPRENANT DU MEGALATRAN ET SON PROMEDICAMENT

(84) Designated Contracting States:
AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
LT LV RO SI

(30) Priority: 21.04.1999 SE 9901442
03.12.1999 SE 9904419

(43) Date of publication of application:
02.05.2002 Bulletin 2002/18

(60) Divisional application:
07120002.6

(73) Proprietor: AstraZeneca AB
151 85 Södertälje (SE)

(72) Inventor: GUSTAFSSON, David
S-431 83 Mölndal (SE)

(56) References cited:
WO-A1-96/16671 WO-A1-97/23499

- H. ERICSSON ET AL.: 'Pharmacokinetics and pharmacodynamics of melagatran, a novel synthetic LMW thrombin inhibitor, in patients with acute DVT' THROMB. HAEMOST. vol. 81, 1999, pages 358 - 363, XP002933665
- DIANE P. IGNASIAK ET AL.: 'Effects of intravenous enoxaparin and intravenous inogatran in an electrolytic injury model of venous thrombosis in the dog' JOURNAL OF THROMBOSIS AND THROMBOLYSIS vol. 6, 1998, pages 199 - 206, XP002933666

EP 1 200 118 B1

Description

Field of the Invention

[0001] This invention relates to a new use of low molecular weight thrombin inhibitors.

Background and Prior Art

[0002] Blood coagulation is the key process involved in both haemostasis (i.e. the prevention of blood loss from a damaged vessel) and thrombosis (i.e. the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).

[0003] Coagulation is the result of a complex series of enzymatic reactions. One of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

[0004] Thrombin is known to play a central role in coagulation. It activates platelets, leading to platelet aggregation, converts fibrinogen into fibrin monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V and factor VIII leading to a "positive feedback" generation of thrombin from prothrombin.

[0005] Effective inhibitors of thrombin are thus known, and/or are expected, to be useful as anticoagulants and therefore useful in the therapeutic treatment of thrombosis and related disorders.

[0006] The early development of low molecular weight inhibitors of thrombin has been described by Claesson in Blood Coagul. Fibrinol. (1994) 5, 411. Low molecular weight thrombin inhibitors have been described more recently in US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596.

[0007] In particular, international patent application WO 94/29336 discloses a group of compounds, including HOOC-CH_2-(*R*)Cgl-Aze-Pab-H (in which Cgl represents cyclohexylglycine, Aze represents *S*-azetidine-2-carboxylic acid and Pab-H represents 4-aminomethyl-amidinobenzene), which is also known as melagatran (see Example 1 of WO 94/29336). International Patent Application WO 97/23499 discloses prodrugs of *inter alia* melagatran.

[0008] None of the above-mentioned documents disclose or suggest the administration of an active thrombin inhibitor in conjunction with a prodrug of that thrombin inhibitor, or indeed in conjunction with a prodrug of any thrombin inhibitor.

[0009] Deep venous thrombosis (DVT) and pulmonary embolism (PE) are major health problems, which may give rise to serious outcomes. In particular, PE may be fatal, or may result in the development of pulmonary hypertension and heart failure from recurrent embolism. DVT may result in post-thrombotic venous insufficiency and ulcers in the affected part of the body (e.g. leg). Both are common conditions, which have a great impact on worldwide healthcare costs.

[0010] There is a considerable incidence of DVT and PE following orthopaedic surgery. For example, in patients undergoing total hip replacement, the incidence of DVT in the absence of thromboprophylaxis may be as high as 45 to 57%. Further, the incidence of proximal DVT may be between 23 and 36 % , and that of fatal PE, 0.34 to 6 % . In patients undergoing total knee replacement in the absence of thromboprophylaxis, the postoperative incidence of DVT is between 40 and 84%, of proximal DVT is between 9 and 20%, and of fatal PE is between 0.2 and 0.7%. In patients undergoing general surgery in the absence of thromboprophylaxis, the postoperative incidence of DVT is about 25%. (Reference: Chest (1998) 114, 531S to 560S.)

[0011] Low-dose, subcutaneous (s.c.) unfractionated heparin is the most widely used current prophylactic treatment for venous thromboembolism resulting from orthopaedic and general surgery. The incidence of DVT after total hip replacement has been shown to be reduced (see Chest reference above).

[0012] The use of low-molecular weight heparin (LMWH) in the prophylaxis of DVT following total hip and knee replacement operations has been shown to further the reduce incidence (when compared to low dose unfractionated heparin), without a concomitant increase in bleeding (see Chest reference above).

[0013] However, prolonged treatment with heparins has been shown to give rise to an increased risk of osteoporosis. Heparins may also give rise to "heparin-induced thrombocytopenia" (HIT), are dependent on the plasma level of the endogenous thrombin inhibitor, antithrombin, and do not inactivate clot-bound thrombin.

[0014] Oral anticoagulants, such as warfarin (a vitamin K antagonist), has also been shown to be effective in reducing DVT after major surgery (see Chest reference above). However, due to the risk of bleeding, and the need for frequent laboratory control, the use of this substance is generally reserved for high risk patients, and/or for long term use. Vitamin K antagonists also demonstrate a notable risk of interaction with other drugs and certain foods, and their use requires

monitoring of the patient's blood coagulation status.

[0015] Antiplatelet agents, such as aspirin, have been shown to have limited efficacy in preventing DVT (see Chest reference above).

[0016] Comparative clinical studies carried out during the course of total hip replacement operations have shown that subcutaneous administration of the thrombin inhibitor hirudin is superior to unfractionated heparin and LMWH in reducing the frequency of total and proximal DVT with no corresponding increase in bleeding (see Eriksson et al in Lancet, 347, 635 (1996) and J. Bone Joint. Surg., Sep., 11 (1996)). However, hirudin is expensive and has an immunogenic potential.

[0017] Thus, there is a need for effective treatments of thrombotic conditions such as DVT.

Disclosure of the Invention

[0018] We have found, surprisingly, that administration of megalatran, a low molecular weight thrombin inhibitor in conjunction with a prodrug according to the formula given in component (b) gives rise to a notable anticoagulant effect.

[0019] According to a first aspect of the invention there is provided a kit of parts comprising components:

(a) a pharmaceutical formulation including melagatran or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
(b) a pharmaceutical formulation including a prodrug of melagatran of the formula

$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH$,

wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

[0020] According to a further aspect of the invention, there is provided a method of making a kit of parts as defined herein, which method comprises bringing a component (a), as defined above, into association with a component (b), as defined above, thus rendering the two components suitable for administration in conjunction with each other.

[0021] By bringing the two components "into association with" each other, we include that components (a) and (b) may be:

(i) provided as separate formulations (i.e. independently of one another), which are subsequently brought together for use in conjunction with each other in combination therapy; or -
(ii) packaged and presented together as separate components of a "combination pack" for use in conjunction with each other in combination therapy.

[0022] Thus, there is further provided a kit of parts comprising:

(1) one of components (a) and (b) as defined herein; together with
(2) instructions to use that component in conjunction with the other of the two components.

[0023] The kits of pans defined herein may comprise more than one formulation including an appropriate quantity/dose of megalatran and/or more than one formulation including an appropriate quantity/dose of respective its prodrug, in order to provide for repeat dosing. If more than one formulation (comprising megalatran or its prodrug) is present, such formulations may be the same, or may be different in terms of the dose of megalatran prodrug, chemical composition and/or physical form.

[0024] The kit of the present invention is suitable for use in a method of treatment of a condition in which inhibition of thrombin is required or desired, which comprises administration of:

(a) a pharmaceutical formulation including melagatran or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
(b) a pharmaceutical formulation including a prodrug of melagatran of the formula

$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH$,

wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab

or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,

which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

[0025] For the avoidance of doubt, as used herein, the term "treatment" includes therapeutic and/or prophylactic treatment.

[0026] "Pharmaceutically acceptable derivatives" of megalatran and its prodrugs includes salts (e.g. pharmaceutically acceptable non-toxic organic or inorganic acid addition salts) and solvates. It will be appreciated that the term pharmaceutically acceptable derivatives of active thrombin inhibitors includes those derivatives that have the same biological function and/or activity as that thrombin inhibitor but, for the purposes of this invention, does not include prodrugs of that thrombin inhibitor.

[0027] By "administration in conjunction with", we include that respective formulations comprising thrombin inhibitor and/or prodrug may be administered, sequentially, separately and/or simultaneously, over the course of treatment of the relevant condition, which condition may be acute or chronic. Preferably, the term includes that the two formulations may be administered (optionally repeatedly) sufficiently closely in time for there to be a beneficial effect for the patient, that is greater, over the course of the treatment of the relevant condition, than if either of the two formulations are administered (optionally repeatedly) alone, in the absence of the other formulation, over the same course of treatment. Determination of whether a combination provides a greater beneficial effect in respect of, and over the course of treatment of, a particular condition, will depend upon the condition to be treated or prevented, but may be achieved routinely by the skilled person.

[0028] Thus, the term "in conjunction with" includes that one or other of the two formulations may be administered (optionally repeatedly) prior to, after, and/or at the same time as, administration with the other component. When used in this context, the terms "administered simultaneously" and "administered at the same time as" include that individual doses of thrombin inhibitor and prodrug are administered within 48 hours (e.g. 24 hours) of each other.

[0029] Components (a) and (b) as described herein may also be presented (i.e. formulated) as a combined preparation (i.e. presented as a single formulation including megalatran and its prodrug).

[0030] Thus, there is further provided a pharmaceutical formulation including megalatran (or a pharmaceutically acceptable salt or solvate thereof) and a prodrug of the formula:

$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH,$$

wherein R^1 represents linear or branched C_{1-6} alkyl and the OH group replaces one of the amidino hydrogens in Pab (or a pharmaceutically acceptable salt or solvate of that prodrug), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

[0031] Preferred low molecular weight peptide-based thrombin inhibitors is $HOOC\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}H$ (known as melagatran; see above and International Patent Application WO 94/29336).

[0032] The term "prodrug" of a megalatran includes any compound that, following oral or parenteral administration, is metabolised *in vivo* to form megalatran in an experimentally-detectable amount, and within a predetermined time (e.g. within a dosing interval of between 6 and 24 hours (i.e. once to four times daily)), following oral or parenteral administration. Preferred prodrugs are those of the formula $R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH$ (see the list of abbreviations above or in WO 97/23499), wherein R^1 represents C_{1-10} alkyl or benzyl, such as linear or branched C_{1-6} alkyl (e.g. C_{1-4} alkyl, especially methyl, propyl and, particularly, ethyl) and the OH group replaces one of the amidino hydrogens in Pab.

[0033] The term "condition in which inhibition of thrombin is required or desired" will be understood by those skilled in the art to include the following:

[0034] The treatment and/or prophylaxis of thrombosis and hypercoagulability in blood and tissues of animals including man. It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases which may be mentioned include inherited or acquired activated protein C resistance, such as the factor V-mutation (factor V Leiden), and inherited or acquired deficiencies in antithrombin III, protein C, protein S, heparin cofactor II. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), homocysteinemi, heparin induced thrombocytopenia and defects in fibrinolysis.

[0035] The treatment of conditions where there is an undesirable excess of thrombin without signs of hypercoagulability, for example in neurodegenerative diseases such as Alzheimer's disease.

[0036] Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis) and systemic embolism usually from the atrium during arterial fibrillation or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of reocclusion (ie thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of rethrombosis after microsurgery and vascular surgery in general.

[0037] Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment when blood is in contact with foreign surfaces in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, septic shock, septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease, cerebral arterial disease, peripheral arterial disease, reperfusion damage, and restenosis after percutaneous trans-luminal angioplasty (PTA).

[0038] Preferred conditions include thrombosis, especially DVT, including distal and proximal DVT. The present invention finds particular utility in the prophylactic treatment of DVT resulting from surgery, such as gastrointestinal, or orthopaedic, surgery (e.g. hip or knee replacement). This includes DVT resulting from immobilisation after surgery.

[0039] In accordance with the invention, megalatran its prodrugs and salts or solvate of either, is suitable to be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally, tracheally, bronchially, topically, by any other parenteral route, or *via* inhalation, in the form of a pharmaceutical preparation comprising the thrombin inhibitor or its prodrug in a pharmaceutically acceptable dosage form. Depending on the disorder, and the patient, to be treated, as well as the route of administration, the compositions may be administered at varying doses.

[0040] Preferred modes of delivery are systemic. For melagatran and salts or solvates thereof, preferred modes of administration are parenteral, more preferably intravenous, and especially subcutaneous. For prodrugs of melagatran, preferred modes of administration are oral.

[0041] In the therapeutic treatment of mammals, and especially humans, megalatran inhibitors, prodrugs of megalatran, and salts or solvates of either will generally be administered as a pharmaceutical formulation in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier, which may be selected with due regard to the intended route of administration and standard pharmaceutical practice.

[0042] Suitable formulations for use in administering thrombin inhibitors are known in the art, and include those known from US Patent N° 4,346,078; International Patent Applications WO 93/11152, WO 93/18060, WO 93/05069, WO 94/20467, WO 94/29336, WO 95/35309, WO 95/23609, WO 96/03374, WO 96/06832, WO 96/06849, WO 96/25426, WO 96/32110, WO 97/01338, WO 97/02284, WO 97/15190, WO 97/30708, WO 97/40024, WO 97/46577, WO 98/06740, WO 97/49404, WO 97/11693, WO 97/24135, WO 97/47299, WO 98/01422, WO 98/57932, WO 99/29664, WO 98/06741, WO 99/37668, WO 99/37611, WO 98/37075, WO 99/00371, WO 99/28297, WO 99/29670, WO 99/40072, WO 99/54313, WO 96/31504, WO 00/01704 and WO 00/08014; and European Patent Applications 648 780, 468 231, 559 046, 641 779, 185 390, 526 877, 542 525, 195 212, 362 002, 364 344, 530 167, 293 881, 686 642, 669 317, 601 459 and 623 596.

[0043] Suitable formulations for use with melagatran, derivatives and prodrugs thereof are described in the literature, for example as described in *inter alia* international patent applications WO 94/29336, WO 96/14084, WO 96/16671, WO 97/23499, WO 97/39770, WO 97/45138, WO 98/16252, WO 99/27912 and WO 99/27913. Otherwise, the preparation of suitable formulations may be achieved non-inventively by the skilled person using routine techniques.

[0044] The amounts of megalatran, its prodrug, or salts or solvates either, in the formulation will depend on the severity of the condition, and on the patient, to be treated, as well as the compound(s) which is/are employed, but may be determined non-inventively by the skilled person.

[0045] Suitable doses of megalatran its prodrugs and salts or solvates of either, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients may be determined routinely by the medical practitioner or other skilled person, and include the respective doses discussed in the prior art documents disclosing thrombin inhibitors that are mentioned hereinbefore, the disclosures in which are hereby incorporated by reference.

[0046] In the case of melagatran, suitable doses of active compound, prodrugs and salts or solvates thereof, in the therapeutic and/or prophylactic treatment of mammalian, especially human, patients include those which give a mean plasma concentration of up to 5 μmol/L, for example in the range 0.001 to 5 μmol/L over the course of treatment of the relevant condition. Suitable doses may thus be in the range 0.1 mg once daily to 25 mg three times daily, and/or up to 100 mg infused parenterally over a 24 hour period, for melagatran, and in the range 0.1 mg once daily to 100 mg three times daily for prodrugs of melagatran including those specifically mentioned hereinbefore.

[0047] In any event, the physician, or the skilled person, will be able to determine the actual dosage which will be most suitable for an individual patient, which is likely to vary with the condition that is to be treated, as well as the age, weight, sex and response of the particular patient to be treated. The above-mentioned dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

[0048] The sequence in which the formulations comprising thrombin inhibitor, and prodrug, may be administered (i.e. whether, and at what point, sequential, separate and/or simultaneous administration takes place) may be determined by the physician or skilled person. For example, the sequence may depend upon many factors that will be evident to the skilled person, such as whether, at any time during the course or period of treatment, one or other of the formulations

cannot be administered to the patient for practical reasons (e.g. the patient is unconscious and thus unable to take an oral formulation comprising either thrombin inhibitor or prodrug).

[0049] For example, in the treatment of thrombosis (e.g. DVT) resulting from surgery, such as gastrointestinal, or orthopaedic, surgery, it is preferred that the formulation comprising melagatran is administered parenterally within two days (e.g. within 24 hours) of surgery (either prior to or after surgery), and particularly immediately prior to (e.g. within 2 hours), and/or within up to 12 hours after, surgery (e.g. at least one hour after surgery), and thereafter for up to between 3 and 7 (e.g. between 0 and 2, such as between 1 and 2) days after that surgery, and that the formulation comprising its prodrug is administered orally within 7 days following that surgery (preferably once administration of melagatran has been terminated) for up to e.g. between 11 and 40 days, preferably 9 days, more preferably up to 8 days.

[0050] The method described herein may have the advantage that, in the treatment of conditions in which inhibition of thrombin is required or desired, it may be more convenient for the physician and/or patient than, be more efficacious than, be less toxic than, have a broader range of activity than, be more potent than, produce fewer side effects than, or that it may have other useful pharmacological properties over, similar methods known in the prior art for the treatment of such conditions.

[0051] The invention is illustrated, but in no way limited, by the following example.

Example 1

Clinical Trial - Melagatran and EtOOC-CH_2-(*R*)Cgl-Aze-Pab-OH Combination Therapy

[0052] A controlled, randomised, parallel group, Swedish multi-centre pilot study was carried out. The study was open with regard to the drugs under evaluation but was blind for the patients, all personnel at the study sites, and for the person monitoring the experiments with regard to the doses of melagatran and the prodrug of melagatran, EtOOC-CH_2-(*R*)Cgl-Aze-Pab-OH (P; see WO 97/23499).

[0053] Dalteparin (Fragmin®; Pharmacia-Upjohn) was used as a reference compound.

[0054] Patients scheduled for primary elective total hip or knee replacement were eligible for inclusion, and were randomly selected into one of three groups, each to receive different doses of melagatran and P, or dalteparin. In all, 135 patients were included in the study, of which 105 patients could be used for evaluation with respect to thromboembolic events using central assessment of locally performed phlebograms.

[0055] About 32 patients in each treatment group were evaluated according to the protocol. A stratified randomisation, by centre and type of surgery, was used to ensure that approximately equal numbers of patients were given each of the drugs under evaluation at all participating centres (in all six centres were used) for both types of surgery (hip or knee). Each centre received study drugs in blocks of four, separately for hips and knees. Within each block, the order of the study drugs was randomised.

[0056] The following formulations were used in the study:

Melagatran - 5, 10 or 20 mg/mL in aqueous saline solution.

P - appropriate weight (see below) in a tablet also comprising 59 to 63 mg corn starch, 115 mg microcrystalline cellulose and 2 mg sodium stearyl fumarate.

[0057] The following doses of melagatran and P were used in the study:

Treatment A - s.c. melagatran (1 mg) b.i.d. for 2 days, followed by oral administration of P (6 mg) b.i.d. for 6 to 9 days.

Treatment B - s.c. melagatran (2 mg) b.i.d. for 2 days, followed by an oral administration of P (12 mg) b.i.d. for 6 to 9 days.

Treatment C - s.c. melagatran (4 mg) b.i.d. for 2 days, followed by an oral administration of P (24 mg) b.i.d. for 6 to 9 days.

[0058] The patients receiving melagatran and P received treatment on the day of surgery. The patient received the first injection after induction of anaesthesia immediately before surgery. For knee-patients, the preoperative melagatran injection was given before tourniquets were applied. The second injection was given in the evening the same day. The patient received one melagatran injection in the morning and one in the evening over the next 24 hours, until oral administration of P, twice daily, started. The first oral dose of P was always taken in the morning. Thus, the total treatment period was between 8 and 11 days.

[0059] Treatment D - dalteparin (Fragmin®): one s.c. injection of 5000 U during the evening of the day before surgery,

continuing with one s.c. injection every evening over a treatment period of 8 to 11 days.

[0060] The plasma concentrations of melagatran were recorded.

[0061] The results of the trial, in terms of the frequencies of thromboembolism after hip or knee surgery, are tabulated below:

	Treatment A		Treatment B		Treatment C		Treatment D	
	(n)	(%)	(n)	(%)	(n)	(%)	(n)	(%)
Outcome	6/29	21	6/24	25	4/24	16	5/27	19

[0062] These data show that a combination of subcutaneously administered melagatran and orally administered P is effective in preventing DVT after orthopaedic surgery.

Claims

1. A kit of parts comprising:

   (a) a pharmaceutical formulation including melagatran or a pharmaceutically acceptable salt or solvate thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier; and
   (b) a pharmaceutical formulation including a prodrug of melagatran of the formula

   $R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH,$

   wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab or a pharmaceutically acceptable salt or solvate of that prodrug, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier,
   which components (a) and (b) are each provided in a form that is suitable for administration in conjunction with the other.

2. A kit of parts as claimed in Claim 1, wherein components (a) and (b) are suitable for sequential, separate and/or simultaneous use in the treatment of a condition in which inhibition of thrombin is required or desired.

3. A kit of parts as claimed in Claim 2, wherein the condition is deep venous thrombosis.

4. A kit of parts as claimed in any one of Claims 1 to 3, wherein R^1 represents methyl, ethyl or propyl.

5. A kit of parts as claimed in Claim 4, wherein R^1 represents ethyl.

6. A kit of parts as claimed in any one of the preceding claims, wherein the formulation comprising melagatran, or salt or solvate thereof, is a parenteral formulation and that comprising the prodrug, or salt or solvate thereof, is an oral formulation.

7. A method of making a kit of parts as defined in any one of Claims 1 to 6, which method comprises bringing a component (a) according to any one of Claims 1 to 6, into association with a component (b) according to any one of Claims 1 to 6, thus rendering the two components suitable for administration in conjunction with each other.

8. A pharmaceutical formulation including melagatran (or a pharmaceutically acceptable salt or solvate thereof) and a prodrug of melagatran of the formula

   $R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH,$

   wherein R^1 represents linear or branched $C_{1\text{-}6}$ alkyl and the OH group replaces one of the amidino hydrogens in Pab (or a pharmaceutically acceptable salt or solvate of that prodrug), in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

9. A pharmaceutical formulation as claimed in Claim 8, wherein R^1 represents methyl, ethyl or propyl.

10. A pharmaceutical formulation as claimed in Claim 9, wherein R^1 represents ethyl.

11. The use of a formulation as defined in any one of Claims 8 to 10, for the manufacture of a medicament for the treatment or prophylaxis of a condition in which inhibition of thrombin is required or desired.

12. A kit of parts as claimed in any one of Claims 2 to 6 in which component (a) of the kit of parts is administered prior to commencement of administration of component (b) of the kit of parts.

13. Use as claimed in Claim 11, wherein the condition is deep venous thrombosis.

14. Use as claimed in Claim 13, wherein the thrombosis results from surgery.

15. Use as claimed in Claim 14, wherein the surgery is gastrointestinal surgery or orthopaedic surgery.

16. A kit of parts as claimed in Claim 12, wherein component (a) of the kit of parts is administered parenterally prior to and/or after surgery and component (b) of the kit of parts is administered orally following that surgery.

17. A kit of parts as claimed in any one of Claims 3 to 6, 12 and 16, wherein the thrombosis results from surgery.

18. A kit of parts as claimed in Claim 17, wherein the surgery is gastrointestinal surgery or orthopaedic surgery.

Patentansprüche

1. Teile-Kit, umfassend:

   (a) eine pharmazeutische Formulierung, einschließlich Melagatran oder eines pharmazeutisch verträglichen Salzes oder Solvates davon, im Gemisch mit einem pharmazeutisch verträglichen Hilfsmittel, Verdünnungsmittel oder Träger; und
   (b) eine pharmazeutische Formulierung, einschließlich eines Prodrugs von Melagatran der Formel

   $$R^1O_2C\text{-}CH_2\text{-(R) Cgl-Aze-Pab-OH,}$$

   wobei R^1 lineares oder verzweigtes $C_{1\text{-}6}$-Alkyl veranschaulicht, und die OH-Gruppe eines der Amidino-Wasserstoff-Atome in Pab ersetzt, oder eines pharmazeutisch verträglichen Salzes oder Solvates dieses Prodrugs, im Gemisch mit einem pharmazeutisch verträglichen Hilfsmittel, Verdünnungsmittel oder Träger, wobei die Komponenten (a) und (b) jeweils in einer Form bereitgestellt werden, die sich zur gemeinsamen Verabreichung eignet.

2. Teile-Kit nach Anspruch 1, wobei sich die Komponenten (a) und (b) für die aufeinander folgende, getrennte und/oder gleichzeitige Verwendung bei der Behandlung eines Zustands eignen, bei dem die Hemmung von Thrombin erforderlich oder gewünscht ist.

3. Teile-Kit nach Anspruch 2, wobei der Zustand eine tiefe Venenthrombose ist.

4. Teile-Kit nach einem der Ansprüche 1 bis 3, wobei R^1 Methyl, Ethyl oder Propyl ist.

5. Teile-Kit nach Anspruch 4, wobei R^1 Ethyl veranschaulicht.

6. Teile-Kit nach einem der vorhergehenden Ansprüche, wobei die Formulierung, die Melagatran, oder ein Salz oder Solvat davon umfasst, eine parenterale Formulierung ist, und diejenige, die das Prodrug, das Salz oder Solvat davon umfasst, eine orale Formulierung ist.

7. Verfahren zur Herstellung eines Teile-Kits nach einem der Ansprüche 1 bis 6, wobei das Verfahren umfasst: das Zusammenbringen einer Komponente (a) nach einem der Ansprüche 1 bis 6 mit einer Komponente (b) nach einem der Ansprüche 1 bis 6, so dass sich die beiden Komponenten zur gemeinsamen Verabreichung eignen.

8. Pharmazeutische Formulierung, einschließlich Melagatran (oder eines pharmazeutisch verträglichen Salzes oder Solvates davon) und eines Prodrugs von Melagatran der Formel

$$R^1O_2C\text{-}CH_2\text{-}(R)Cgl\text{-}Aze\text{-}Pab\text{-}OH,$$

wobei R^1 lineares oder verzweigtes $C_{1\text{-}6}$-Alkyl veranschaulicht, und die OH-Gruppe eines der Amidino-Wasserstoff-Atome in Pab ersetzt, oder eines pharmazeutisch verträglichen Salzes oder Solvates dieses Prodrugs, im Gemisch mit einem pharmazeutisch verträglichen Hilfsmittel, Verdünnungsmittel oder Träger.

9. Pharmazeutische Formulierung nach Anspruch 8, wobei R^1 Methyl, Ethyl oder Propyl veranschaulicht.

10. Pharmazeutische Formulierung nach Anspruch 9, wobei R^1 Ethyl veranschaulicht.

11. Verwendung einer Formulierung nach einem der Ansprüche 8 bis 10, zur Herstellung eines Medikamentes zur Behandlung oder Prophylaxe eines Zustands, in dem die Hemmung von Thrombin erforderlich oder gewünscht ist.

12. Teile-Kit nach einem der Ansprüche 2 bis 6, wobei die Komponente (a) des Teile-Kits vor dem Beginn der Verabreichung von Komponente (b) des Teile-Kits verabreicht wird.

13. Verwendung nach Anspruch 11, wobei der Zustand tiefe Venenthrombose ist.

14. Verwendung nach Anspruch 13, wobei die Thrombose von einer Operation herrührt.

15. Verwendung nach Anspruch 14, wobei die Operation eine gastrointestinale Operation oder orthopädische Operation ist.

16. Teile-Kit nach Anspruch 12, wobei die Komponente (a) des Teile-Kits vor und/oder nach der Operation verabreicht wird und die Komponente (b) des Teile-Kits oral nach dieser Operation verabreicht wird.

17. Teile-Kits nach einem der Ansprüche 3 bis 6, 12 und 16, wobei die Thrombose aus der Operation hervorgeht.

18. Teile-Kits nach Anspruch 17, wobei die Operation eine gastrointestinale Operation oder eine orthopädische Operation ist.

Revendications

1. Trousse à compartiments comprenant :

(a) une préparation pharmaceutique comprenant du mélagatran ou bien un sel ou un solvate de celui-ci, acceptable d'un point de vue pharmaceutique, en mélange avec un adjuvant, un diluant ou un véhicule acceptable d'un point de vue pharmaceutique ; et
(b) une préparation pharmaceutique comprenant un promédicament de mélagatran de formule

$$R^1O_2C\text{-}CH_2\text{-}(R)\ Cgl\text{-}Aze\text{-}Pab\text{-}OH,$$

dans laquelle R^1 représente un alkyle en $C_{1\text{-}6}$ linéaire ou ramifié et le groupe OH remplace l'un des hydrogènes de l'amidino dans le Pab, ou bien un sel ou un solvate de ce promédicament, acceptable d'un point de vue pharmaceutique, en mélange avec un adjuvant, un diluant ou un véhicule acceptable d'un point de vue pharmaceutique, les composants (a) et (b) étant fournis chacun sous une forme qui est appropriée pour être administrée l'une avec l'autre.

2. Trousse à compartiments selon la revendication 1, dans laquelle les composants (a) et (b) sont appropriés pour une utilisation séquentielle, séparée et/ou simultanée dans le traitement d'une condition dans laquelle une inhibition de la thrombine est requise ou souhaitée.

3. Trousse à compartiments selon la revendication 2, dans laquelle la condition est une thrombose veineuse profonde.

4. Trousse à compartiments selon l'une quelconque des revendications 1 à 3, dans laquelle R^1 représente un méthyle, un éthyle ou un propyle.

5. Trousse à compartiments selon la revendication 4, dans laquelle R^1 représente un éthyle.

6. Trousse à compartiments selon l'une quelconque des revendications précédentes, dans laquelle la préparation comprenant du mélagatran ou bien un sel ou un solvate de celui-ci est une préparation parentérale et celle comprenant le promédicament ou bien un sel ou un solvate de celui-ci est une préparation orale.

7. Procédé d'élaboration d'une trousse à compartiments, selon l'une quelconque des revendications 1 à 6, lequel procédé comprend l'étape consistant à amener en association un composant (a), selon l'une quelconque des revendications 1 à 6, avec un composant (b), selon l'une quelconque des revendications 1 à 6, en rendant ainsi les deux composants appropriés pour être administrés conjointement.

8. Préparation pharmaceutique comprenant du mélagatran (ou bien un sel ou un solvate de celui-ci acceptable d'un point de vue pharmaceutique) et un promédicament de mélagatran de formule

$$R^1O_2C\text{-}CH_2\text{-}\ (R)\ Cgl\text{-}Aze\text{-}Pab\text{-}OH,$$

dans laquelle R^1 représente un alkyle en $C_{1\text{-}6}$ linéaire ou ramifié et le groupe OH remplace l'un des hydrogènes de l'amidino dans le Pab (ou bien un sel ou un solvate de ce promédicament acceptable d'un point de vue pharmaceutique) en mélange avec un adjuvant, un diluant ou un véhicule acceptable d'un point de vue pharmaceutique.

9. Préparation pharmaceutique selon la revendication 8, dans laquelle R^1 représente un méthyle, un éthyle ou un propyle.

10. Préparation pharmaceutique selon la revendication 9, dans laquelle R^1 représente un éthyle.

11. Utilisation d'une préparation, selon l'une quelconque des revendications 8 à 10, pour la fabrication d'un médicament destiné au traitement ou à la prophylaxie d'une condition dans laquelle une inhibition de la thrombine est requise ou souhaitée.

12. Trousse à compartiments selon l'une quelconque des revendications 2 à 6, dans laquelle le composant

    (a) de la trousse à compartiments est administré avant le début de l'administration du composant
    (b) de la trousse à compartiments.

13. Utilisation selon la revendication 11, dans laquelle la condition est une thrombose veineuse profonde.

14. Utilisation selon la revendication 13, dans laquelle la thrombose résulte d'une chirurgie.

15. Utilisation selon la revendication 14, dans laquelle la chirurgie est une chirurgie gastro-intestinale ou une chirurgie orthopédique.

16. Trousse à compartiments selon la revendication 12,
dans laquelle le composant (a) de la trousse à compartiments est administré par voie parentérale avant et/ou après une chirurgie et le composant (b) de la trousse à compartiments est administré oralement après cette chirurgie.

17. Trousse à compartiments selon l'une quelconque des revendications 3 à 6, 12 et 16, dans laquelle la thrombose résulte d'une chirurgie.

18. Trousse à compartiments selon la revendication 17,
dans laquelle la chirurgie est une chirurgie gastro-intestinale ou une chirurgie orthopédique.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US 4346078 A [0006] [0042]
- WO 9311152 A [0006] [0042]
- WO 9318060 A [0006] [0042]
- WO 9305069 A [0006] [0042]
- WO 9420467 A [0006] [0042]
- WO 9429336 A [0006] [0007] [0007] [0031] [0042] [0043]
- WO 9535309 A [0006] [0042]
- WO 9523609 A [0006] [0042]
- WO 9603374 A [0006] [0042]
- WO 9606832 A [0006] [0042]
- WO 9606849 A [0006] [0042]
- WO 9625426 A [0006] [0042]
- WO 9632110 A [0006] [0042]
- WO 9701338 A [0006] [0042]
- WO 9702284 A [0006] [0042]
- WO 9715190 A [0006] [0042]
- WO 9730708 A [0006] [0042]
- WO 9740024 A [0006] [0042]
- WO 9746577 A [0006] [0042]
- WO 9806740 A [0006] [0042]
- WO 9749404 A [0006] [0042]
- WO 9711693 A [0006] [0042]
- WO 9724135 A [0006] [0042]
- WO 9747299 A [0006] [0042]
- WO 9801422 A [0006] [0042]
- WO 9857932 A [0006] [0042]
- WO 9929664 A [0006] [0042]
- WO 9806741 A [0006] [0042]
- WO 9937668 A [0006] [0042]
- WO 9937611 A [0006] [0042]
- WO 9837075 A [0006] [0042]
- WO 9900371 A [0006] [0042]
- WO 9928297 A [0006] [0042]
- WO 9929670 A [0006] [0042]
- WO 9940072 A [0006] [0042]
- WO 9954313 A [0006] [0042]
- WO 9631504 A [0006] [0042]
- WO 0001704 A [0006] [0042]
- WO 0008014 A [0006] [0042]
- WO 9723499 A [0007] [0032] [0043] [0052]
- EP 648780 A [0042]
- EP 468231 A [0042]
- EP 559046 A [0042]
- EP 641779 A [0042]
- EP 185390 A [0042]
- EP 526877 A [0042]
- EP 542525 A [0042]
- EP 195212 A [0042]
- EP 362002 A [0042]
- EP 364344 A [0042]
- EP 530167 A [0042]
- EP 293881 A [0042]
- EP 686642 A [0042]
- EP 669317 A [0042]
- EP 601459 A [0042]
- EP 623596 A [0042]
- WO 9614084 A [0043]
- WO 9616671 A [0043]
- WO 9739770 A [0043]
- WO 9745138 A [0043]
- WO 9816252 A [0043]
- WO 9927912 A [0043]
- WO 9927913 A [0043]

Non-patent literature cited in the description

- ERIKSSON et al. *Lancet*, 1996, vol. 347, 635 [0016]
- *J. Bone Joint. Surg.*, 11 September 1996 [0016]