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(54) Title: PHARMACEUTICAL SYSTEM FOR TRANSDERMAL ADMINISTRATION OF A Cl -ESTERASE INHIBITOR

(57) Abstract: The present invention relates to the field of medicine, specifically to a pharmaceutical system for transdermal adminis¬tration of a pharmacologically active ingredient having the effect of a Cl esterase inhibitor, such as a Cl esterase inhibitor.

PHARMACEUTICAL SYSTEM FOR TRANSDERMAL ADMINISTRATION OF A C1-ESTERASE INHIBITOR

Field of the invention

The present invention relates to the field of medicine, specifically to a pharmaceutical system for transdermal administration of a pharmacologically active ingredient.

Background of the invention

Human C1 inhibitor, also known as C1 esterase inhibitor, is a well-known and identified substance. C1 inhibitor belongs to the superfamily of serine proteinase inhibitors and is the only inhibitor of Clr and Cls of the complement system and is the major inhibitor of factor XIIa and kallikrein of the contact system. In addition, C1 inhibitor inhibits also other serine proteases of the coagulation and fibrinolytic systems like factor XI, tissue type plasminogen activator and plasmin (Schapira M. et al. 1985, Complement 2:1 11; Davis A.E. 1988, Ann. Rev. Immunol. 6:595). C1 inhibitor is encoded by a single gene on chromosome 11 and consists of 8 exons and 7 introns. The entire genomic sequence is known and codes for a protein of 500 amino acids, including a 22-amino acid signal sequence (Carter P. et al. 1988, Euro. J. Biochem. 173; 163). Plasma C1 inhibitor is a glycoprotein of approximately105 kDa and is heavily glycosylated. Human C1 esterase inhibitor is *inter alia* used for the treatment of hereditary angioedema (HAE) and for treatment and prevention of ischemia-reperfusion injury. Pharmaceutical grade human C1 esterase inhibitor can be derived from human plasma or can be produced recombinantly in tissue culture cells (such as Chinese Hamster Ovarian (CHO) cells) or in transgenic animals (such as transgenic rabbits).

C1 inhibitor is usually administered intravenously and, more recently, subcutaneously (see, e.g., WO2014145519). Transdermal delivery would represent an attractive alternative to intravenous or subcutaneous delivery of C1 inhibitor, as it may enhance effectivity. However, it is a challenge to deliver a composition comprising the C1 esterase inhibitor via the transdermal route, since the typical doses of 25, 50 or 100U per kg bodyweight may require over 10ml of composition to be administered. Accordingly, there is a need for an improved transdermal delivery system of C1 esterase inhibitor.

Summary of the invention

The invention provides for a pharmaceutical system for transdermal administration of the pharmacologically active compound C1 esterase inhibitor, comprising a surface layer and a C1 esterase inhibitor.

The invention further provides for the use of a C1 esterase inhibitor as described herein for the manufacture of a pharmaceutical system according to the invention.

The invention further provides for a method of treatment of a subject suffering from or susceptible to a condition related to acute or chronic C1 esterase inhibitor deficiency, comprising administration of a pharmaceutical system according to the invention to the subject.

Detailed description of the invention

The inventors have arrived at the surprising finding that it is possible to deliver the required amount of C1 esterase inhibitor transdermally by using a pharmaceutical delivery system for transdermal administration. Accordingly, in a first aspect the invention provides for a pharmaceutical system for transdermal administration of a pharmacologically active compound having the effect of a C1 esterase inhibitor, comprising a surface layer and the pharmacologically active compound having the effect of a C1 esterase inhibitor, such as a C1 esterase inhibitor. The pharmaceutical system for transdermal administration is herein interchangeably referred to as the pharmaceutical system according to the invention which is a system to provide transdermal delivery of the C1 esterase inhibitor to a subject. The pharmaceutical system according to the invention preferably comprises the pharmacologically active compound having the effect of a C1 esterase inhibitor. The pharmacologically active compound having the effect of a C1 esterase inhibitor is herein interchangeably referred to as the C1 (esterase) inhibitor according to the invention for purpose of conciseness; in the claims C1 esterase inhibitor means C1 esterase inhibitor. A pharmaceutical system according to the invention may be a pharmaceutical patch for transdermal administration which is herein interchangeably referred to as the pharmaceutical patch according to the invention and which is a system for placement on the skin of a subject to provide transdermal delivery of the C1 esterase inhibitor to the subject. A pharmaceutical system according to the invention may be an applicator device comprising a reservoir with C1 esterase inhibitor. The pharmacologically active compound having the effect of a C1 esterase inhibitor can be a C1 esterase inhibitor, an antibody to C1 esterase, an antibody to Kallikrein, a Kallikrein B1 or B2 receptor blocker or an antibody to F XII. A preferred pharmacologically active compound is a C1 esterase inhibitor.

During storage, the pharmaceutical patch according to the invention will typically be located on a (re)detachable protective layer from which it can be removed immediately before application to the surface of the subject's skin. Protected this way, it may be stored in a blister pack or a sealed bag.

Accordingly, in the embodiments of the invention, the pharmaceutical patch according to the invention can comprise an adhesive layer and a removable protective layer, wherein the adhesive layer is located between the surface layer and the removable protective layer. The adhesive layer and the protective layer may be any known to the person skilled in the art; they may e.g. be as described in EP2809307, in EP2908873 or in WO2014195352, which are herein incorporated by reference. The C1 esterase inhibitor may be present in the surface layer, in the adhesive layer and/or in a (micro)reservoir. Accordingly, in the pharmaceutical patch according to the invention at least a portion of the C1 esterase inhibitor is contained in the adhesive layer, in the surface layer and/or in a (micro)reservoir within the pharmaceutical patch according to the

invention. In the embodiments of the invention, the pharmaceutical patch according to the invention can further comprise a back layer which is impermeable to the C1 esterase inhibitor. The pharmaceutical patch according to the invention can be of the type where the C1 esterase inhibitor diffuses from the patch into the skin in a passive way, which can be facilitated by helper agents that aid the C1 esterase inhibitor to penetrate the skin, such as, but not limited, to dimethyl sulfoxide (DSMO), salicylate and the agents listed in EP2809307, in EP2908873 and in WO20141 95352. Alternatively, or in combination with the previous embodiments, the pharmaceutical system according to the invention may further comprise microneedles. In case the pharmaceutical system according to the invention is a patch, the microneedles can be on the surface layer of the patch. The system may have a reservoir system operably-linked to the microneedles and comprising at least part of the C1 esterase inhibitor. The reservoir may have any suitable size to accommodate the required amount of C1 esterase inhibitor; for a patch, it may be a microreservoir. Microneedle systems may comprise distinct applicator devices or may be patches (sometimes also referred to as microneedle arrays); both are known in the art, e.g. from WO20151 17938, WO2016162449, WO20161 18459, W02006055795, W02007002521 , WO201 3055638, WO2013055641 , W02007002522, WO2012122162 and W02010059605, which are herein incorporated by reference. The pharmaceutical system according to the invention may comprise microneedles that are hollow (such as e.g. in WO201 0059605), microneedles that are solid (such as e.g. in WO20161 18459, W02007002522, WO2012122162, W02006055795, W02007002521 , WO201 3055638 and WO20 1305564 1) and/or microneedles that are dissolving and/or hydrogel forming (such as e.g. in Arya et al, 2017 and Ita et al, which is herein incorporated by reference). The microneedles may be coated with the C1 esterase inhibitor. In a pharmaceutical patch comprising hollow microneedles, the C1 esterase inhibitor may be present in the needles, may be present in a (micro)reservoir or both. In a pharmaceutical patch comprising microneedles that are dissolving and/or hydrogel forming, the C1 esterase inhibitor may be present in the needles, may be present in a (micro)reservoir or both. In the latter option, part of the C1 esterase inhibitor will be present in the dissolving and/or hydrogel forming needles and part of the C1 esterase inhibitor will be present in the (micro)reservoir.

In the embodiments of the invention, the pharmaceutical system according to the invention can be a microneedle patch as defined in WO20151 17938 and WO2016162449 or is a microneedle device as defined in WO20161 18459, W02007002522, WO2012122162, W02006055795, W02007002521 , WO201 3055638, WO20 13055641 and/or W02010059605, comprising the C1 esterase inhibitor according to the invention.

In the embodiments of the invention, if the pharmaceutical system according to the invention is a microneedle applicator system (e.g. one according to W02006055795, W02007002521 , WO201 3055638, WO201 3055641 or W02007002522), the C1 esterase inhibitor can be present in a separate reservoir, which may also be referred as a cartridge, vial or container. The separate reservoir enables to keep the C1 esterase inhibitor separate from the applicator, e.g. the C1 esterase inhibitor reservoir can be kept refrigerated while the applicators can be kept at room temperature. The applicator may be a system that uses separate arrays of microneedles. This

enables single use of the microneedle arrays and multiple use of the applicator device. The separate reservoir comprising the C1 esterase inhibitor may be into in a spring-loaded applicator where relaxation of the spring will push the C1 esterase inhibitor through the microneedles into the skin. All these devices are known to the person skilled in the art and are exemplified in the references herein. When the C1 esterase inhibitor is in lyophilized form, it may be reconstituted by addition of an appropriate amount of an appropriate pharmaceutical grade liquid. In the embodiments of the invention, the reconstitution can be performed shortly before administration. In an embodiment, the C1 esterase inhibitor is present in a cartridge together with the appropriate pharmaceutical liquid for reconstitution, wherein the C1 esterase inhibitor and the liquid are separated by a membrane. Shortly before administration, the membrane is disrupted in a first action, thus allowing mixing of the C1 esterase inhibitor with the pharmaceutical liquid for reconstitution and subsequent reconstitution of the C1 esterase inhibitor. In a second action, the reconstituted C1 esterase inhibitor is administered to the skin of the subject, e.g. by a spring-loaded applicator as described here above. The pharmaceutical liquid can be an aqueous liquid and optionally a buffered aqueous liquid.

In the pharmaceutical patch according to the invention, the surface layer of the patch can have a surface area of at least about 0.5, about 0.7, about 0.75, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 2, about 3, about 4, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95 or about 100 cm^2. In the embodiments of the invention, the surface layer of the patch can have a surface area of about 0.5, about 0.7, about 0.75, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 2, about 3, about 4, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95 or about 100 cm^2. In the embodiments of the invention, the surface layer of the patch can have a surface area of at least 0.5, 0.7, 0.75, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2. In yet another alternative embodiment, in the pharmaceutical patch according to the invention, the surface layer of the patch has a surface area of 0.5, 0.7, 0.75, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2.

In the embodiments of the invention, the pharmaceutical system according to the invention can have a surface area of at least about 0.5, about 0.7, about 0.75, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 2, about 3, about 4, about 5, about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95 or about 100 cm^2. Preferably, such pharmaceutical system is a microneedle system according to the invention.

In the embodiments of the invention, the pharmaceutical system according to the invention can have a surface area of about 0.5, about 0.7, about 0.75, about 0.8, about 0.9, about 1.0, about 1.1, about 1.2, about 1.3, about 1.4, about 1.5, about 2, about 3, about 4, about 5, about 10, about 15,

about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 55, about 60, about 65, about 70, about 75, about 80, about 85, about 90, about 95 or about 100 cm^2. Preferably, such pharmaceutical system is a microneedle system according to the invention.

In the embodiments of the invention, the pharmaceutical system according to the invention can have a surface area of at least 0.5, 0.7, 0.75, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2. Preferably, such pharmaceutical system is a microneedle system according to the invention.

In the embodiments of the invention, the pharmaceutical system according to the invention can have a surface area of 0.5, 0.7, 0.75, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2. Preferably, such pharmaceutical system is a microneedle system according to the invention.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise at least about 25, about 50, about 60, about 75, about 80, about 100, about 120, about 140, about 150, about 160, about 180, about 200, about 210, about 220, about 240, about 250, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1000, about 1100, about 1200, about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, about 1900, about 2000, about 2100, about 2200, about 2300, about 2400, about 2500, about 3000, about 3500, about 4000, about 4500, about 5000, about 5500, about 6000, about 6500, about 7000, about 7500, or at least about 8000 units of C1 esterase inhibitor. In the embodiments of the invention, the pharmaceutical system according to the invention can comprise about 25, about 50, about 60, about 75, about 80, about 100, about 120, about 140, about 150, about 160, about 180, about 200, about 210, about 220, about 240, about 250, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1000, about 1100, about 1200, about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, about 1900, about 2000, about 2100, about 2200, about 2300, about 2400, about 2500, about 3000, about 3500, about 4000, about 4500, about 5000, about 5500, about 6000, about 6500, about 7000, about 7500, or about 8000 units of C1 esterase inhibitor. In the embodiments of the invention, the pharmaceutical system according to the invention can comprise at least 25, 50, 60, 75, 80, 100, 120, 140, 150, 160, 180, 200, 210, 220, 240, 250, 300, 400, 500, 600, 700, 800, 900, 100, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, or at least 8000 units of C1 esterase inhibitor.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise 25, 50, 60, 75, 80, 100, 120, 140, 150, 160, 180, 200, 210, 220, 240, 250, 300, 400, 500, 600, 700, 800, 900, 1000. 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, 2100, 2200, 2300, 2400, 2500, 3000, 3500, 4000, 4500, 5000, 5500, 6000, 6500, 7000, 7500, or 8000 units of C1 esterase inhibitor.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise at least about 25, about 50, about 60, about 75, about 80, about 100, about 120, about 140, about 150, about 160, about 180, about 200, about 210, about 220, about 240, or about 250 units of C1 esterase inhibitor/cm^2.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise about 25, about 50, about 60, about 75, about 80, about 100, about 120, about 140, about 150, about 160, about 180, about 200, about 210, about 220, about 240, or about 250 units of C1 esterase inhibitor/cm^2.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise at least 25, 50, 60, 75, 80, 100, 120, 140, 150, 160, 180, 200, 210, 220, 240, 250 units of C1 esterase inhibitor/cm^2.

In the embodiments of the invention, the pharmaceutical system according to the invention can comprise 25, 50, 60, 75, 80, 100, 120, 140, 150, 160, 180, 200, 210, 220, 240, 250 units of C1 esterase inhibitor/cm^2.

Herein, one unit (U) of C1 esterase inhibitor is the amount of C1 esterase inhibitor present in 1 milliliter of human plasma. One such unit corresponds to approximately 275 microgram plasma-derived or recombinant human C1 esterase inhibitor.

When the C1 esterase inhibitor is present in an aqueous solution, the volume of the solution may be at most about 0.5ml, about 1ml, aboutl .5ml, about 2ml, about 3ml, about 4ml, or at most about 5ml. Alternatively, the volume of the solution is at most 0.5ml, 1ml, 1.5ml, 2ml, 3ml, 4ml, or at most 5ml. Alternatively, the volume of the solution is about 0.5ml, about 1ml, about 1.5ml, about2ml, about 3ml, about 4ml, or about 5ml. Alternatively, the volume of the solution is 0.5ml, 1ml, 1.5ml, 2ml, 3ml, 4ml, or 5ml. In the embodiments of the invention, the amount of C1 esterase inhibitor can be 2100 units in 2 or 3ml. The invention provides for a vial comprising about or exactly 700, 1400 or 2100 units of lyophilized C1 esterase inhibitor. In the embodiments of the invention, the C1 esterase inhibitor can be the as described in W00 1/57079, which is herein incorporated by reference. The invention further provides for a vial comprising about or exactly 2100 units of reconstituted C1 esterase inhibitor in 2, 3, 4 or 5ml reconstitution liquid; in one embodiment, the C1 esterase inhibitor is as described in W00 1/57079.

The C1 esterase inhibitor may be any C1 esterase inhibitor of pharmaceutical grade known to the person skilled in the art. In the embodiments of the invention, the C1 esterase inhibitor can be a plasma-derived C1 esterase inhibitor. In the embodiments of the invention, the C1 esterase inhibitor can be a recombinant C1 esterase inhibitor. In the embodiments of the invention, the C1 esterase inhibitor may have an amino acid sequence that is substantially identical to the amino acid sequence of human plasma-derived C1 esterase inhibitor. The recombinant C1 esterase inhibitor may be any recombinant C1 esterase inhibitor known the person skilled in the art. It may be produced recombinantly in microbial cells, such as tissue culture cells. A preferred tissue culture cell is a mammalian tissue culture cell, such as a Chinese Hamster Ovarian (CHO) cell or a human tissue culture cell (see e.g. WO201 6/081 889, which is herein incorporated by reference). The recombinant C1 esterase inhibitor may be produced in transgenic animals. In the embodiments of the invention, the recombinant C1 esterase inhibitor can be produced in a transgenic non-human mammal, selected from a mouse, goat, bovine, sheep, porcine or an animal from the order *Lagomorpha,* such as *Leporadae,* including a rabbit. In the embodiments

of the invention, the recombinant C1 esterase inhibitor can be produced according to the methods described in W001/57079, which is herein incorporated by reference.

In the embodiments of the invention, the C1 esterase inhibitor may be a modified C1 esterase inhibitor as compared to human plasma-derived C1 esterase inhibitor. The C1 esterase inhibitor may be modified with regards to its amino acid sequence including deletions, elongations, truncations, rearrangements as well as fusions with other natural or synthetic molecules. The C1 esterase inhibitor may be modified to modulate the plasma half-life of the C1 esterase inhibitor. A specific modified C1 esterase inhibitor is conjugated to enhance the plasma half-life. Another specific C1 esterase inhibitor is a conjugated C1 esterase inhibitor according to WO201 7/1 76798, which is herein incorporated by reference, which may be a polysialic acid (PSA)-conjugated C1 esterase inhibitor, or a polyethylene glycol (PEG)-conjugated C1 esterase inhibitor. The modification of the C1 esterase inhibitor may be a modified carbohydrate structure as compared to human plasma-derived C1 esterase inhibitor. A specific modified C1 esterase inhibitor has a reduced level of terminal sialic acid residues as compared to plasma derived C1 esterase inhibitor, wherein said reduced level of terminal sialic acid residues may result in a plasma half-life of less than 6 hours. The C1 esterase inhibitor having a reduced level of terminal sialic acid residues as compared to plasma derived C1 esterase inhibitor may be a C1 esterase inhibitor according to W001/57079, W02004100982 and W02007073186 which are herein incorporated by reference.

The C1 esterase inhibitor according to the invention may be present as such in the pharmaceutical system according to the invention or may be comprised in a pharmaceutical composition. The pharmaceutical composition may comprise pharmaceutically accepted excipients and/or may comprise a further pharmaceutically active compound.

In an embodiment, other compounds may be used that have the same effect as a C1 esterase inhibitor such as an antibody to C1 esterase, an antibody to Kallikrein, a Kallikrein B1 or B2 receptor blocker or antibody to F XII.

In a second aspect the invention provides for the use of a C1 inhibitor according to the invention for the manufacture of a pharmaceutical system according to the invention. Typically, the pharmaceutical system will be assembled according to a method known to the person skilled in the art (e.g. as described in WO20151 17938, WO2016162449, WO20161 18459, W02007002522, WO2012122162, W02010059605, W02006055795, W02007002521 , WO2013055638 and/or WO2013055641) and during or after assembly, the C1 esterase inhibitor as defined herein may be comprised into the pharmaceutical system. The features of this aspect of the invention can be the features of the first aspect of the invention.

In a third aspect the invention provides for the medical use of the pharmaceutical system according to the invention, including but not limited to methods of treatment comprising administration of the pharmaceutical system, use of the pharmaceutical system for treatment, a pharmaceutical system according to the invention for use as a medicament and use of the

pharmaceutical system for the manufacture of a medicament to treat a stated condition. The features of this aspect of the invention can be the features of the first and second aspect of the invention.

The medical use herein may thus interchangeably be formulated as a pharmaceutical system according to the invention for use as a medicament for treatment of a subject for a stated condition but can equally be formulated as a method of treatment of a subject for a stated condition using a pharmaceutical system according to the invention, use of a pharmaceutical system according to the invention in the preparation of a medicament to treat a stated condition in a subject and use of a pharmaceutical system according to the invention for the treatment of a subject for a stated condition. Such medical uses are all envisaged by the present invention. Treatment may be therapeutic and/or prophylactic; when the term "treatment" is used, it can thus also be construed as "prevention" or "delay".

Accordingly, there is provided a method of treatment of a subject suffering from or susceptible to a condition related to acute or chronic C1 esterase inhibitor deficiency, comprising administration of a pharmaceutical system according to the invention to the subject. The subject in the invention may by an animal subject, such as a mammal including cattle, domestic animals like a dog or a cat, or may be a human subject. The condition related to acute or chronic C1 esterase inhibitor deficiency can be hereditary angioedema (HAE) which can be Type I and II as well as angioedema Type III and IV, which may be chronic or acute. Another condition to be treated or prevented may be ischemia-reperfusion injury. Accordingly, the invention provides for a method of treatment of a subject suffering from hereditary angioedema (HAE), which may be chronic or acute, comprising administration of a pharmaceutical system according to the invention. In addition, the invention provides for a method of treatment (or prevention) of a subject suffering from or at risk of ischemia-reperfusion injury, comprising administration of a pharmaceutical system according to the invention.

In the medical use according to the invention, the pharmaceutical system can be a pharmaceutical patch according to the invention and is fixed to the skin of the subject. To facilitate transdermal administration of the C1 esterase inhibitor, some pressure can be applied on the pharmaceutical patch. Accordingly, subsequent to fixation, pressure can be applied to the pharmaceutical patch for a certain time such as, for at least 10%, 20%, 30%, 50%, 60%, 70%, 80%, 90% of the time that the pharmaceutical patch is kept on the subject. In an embodiment, pressure is applied during the entire time that the pharmaceutical patch is kept on the subject.

The pharmaceutical patch can be applied to any convenient place on the subject, such as the back, shoulder, nates, buttocks or back of the thigh of the subject, to allow the body weight of the subject to apply pressure to the pharmaceutical patch. In the embodiments of the invention, the pharmaceutical patch can be kept on the subject for at least about half an hour, about one hour, about two, hours, about three hours, about four hours, about five hours, at least about six hours, at least about eight hours, at least about ten hours, at least about twelve hours. When applied to the back, shoulder, nates, buttocks or back of the thigh of the subject, pressure can

be applied to the pharmaceutical patch by lying on the back and/or shoulder, or sitting such that pressure is applied on the back, shoulder, nates, buttocks or back of the thigh comprising the pharmaceutical patch according to the invention. The dose transferred by the patch to the subject can be about 5, about 10, about 15m about 20, about 25, about 50 or about 100 units C1 esterase inhibitor per kg bodyweight. In an embodiment, at least about 25 units per kg bodyweight is transferred. In an embodiment, the dose transferred to the subject is 5, 10, 15, 20, 25, 50 or 100 units C1 esterase inhibitor. In an embodiment, at least 25 units per kg bodyweight is transferred. In an embodiment a total dose of about or exactly 700, 1400 or 2100 units is transferred to the subject.

The invention further provides for a method of treatment according to the invention, wherein the pharmaceutical system is a microneedle system according to the invention and wherein the microneedle system discharges the C1 esterase inhibitor load into the skin of the subject. In an embodiment, about or exactly 5, 10, 15, 20, 25, 50 or 100 units of C1 esterase inhibitor per kg bodyweight or a total dose of about or exactly 2100 units of C1 esterase inhibitor is transferred to the subject. In this medical use according to the invention, examples of the microneedle system that can be used are described in W02006055795, W02007002521, WO201 3055638, WO201 3055641 and/or W02007002522.

Unless otherwise indicated each embodiment as described herein may be combined with another embodiment as described herein.

Definitions

In this document and in its claims, the verb "to comprise" and its conjugations is used in its non¬limiting sense to mean that items following the word are included, but items not specifically mentioned are not excluded. In addition, the verb “to consist” may be replaced by “to consist essentially of” meaning that a product or a composition or a nucleic acid molecule or a peptide or polypeptide of a nucleic acid construct or vector or cell as defined herein may comprise additional component(s) than the ones specifically identified; said additional component(s) not altering the unique characteristic of the invention. In addition, reference to an element by the indefinite article "a" or "an" does not exclude the possibility that more than one of the elements is present, unless the context clearly requires that there be one and only one of the elements. The indefinite article "a" or "an" thus usually means "at least one".

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

Embodiments of the invention

1. A pharmaceutical system for transdermal administration of a pharmacologically active compound having the effect of a C1 esterase inhibitor, comprising a surface layer and the

pharmacologically active compound having the effect of a C1 esterase inhibitor, such as a C1 esterase inhibitor.

2. A pharmaceutical system according to embodiment 1 wherein the pharmaceutical system is a patch and further comprises an adhesive layer and a removable protective layer, wherein the adhesive layer is located between the surface layer and the removable protective layer.

3. A pharmaceutical patch according to embodiment 2, wherein at least a portion of the C1 esterase inhibitor is contained in the adhesive layer and/or in the surface layer.

4. A pharmaceutical patch according to embodiment 2 or 3, further comprising a back layer which is impermeable to the C1 esterase inhibitor.

5. The pharmaceutical system according to any one of embodiments 2 to 4, further comprising microneedles, in case of a patch, the microneedles are on the surface layer optionally comprising a reservoir system operably linked to the microneedles comprising at least a part of the C1 esterase inhibitor.

6. The pharmaceutical patch according to embodiment 5, wherein the microneedles are hollow, solid, dissolving and/or hydrogel forming microneedles.

7. The pharmaceutical system according to any one of embodiments 1 to 74 or 5, wherein the pharmaceutical system is a microneedle patch as defined in WO20151 17938 or WO201 6162449 or wherein the pharmaceutical system is a microneedle device as defined in WO20161 18459, W02006055795, W02007002521 , W02007002522, WO2012122162, WO201 3055638, WO201 3055641 or WO201 0059605.

8. The pharmaceutical system according to any of embodiments 1 to 7, wherein the surface layer of the patch has a surface area of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50,. 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2.

9. The pharmaceutical system according to any of embodiments 1 to 8, comprising at least about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1000, about 1100, about 1200, about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, about 1900, about 2000, about 2100, about 2200, about 2300, about 2400, about 2500, about 3000, about 3500, about 4000, about 4500, about 5000, about 5500, about 6000, about 6500, about 7000, about 7500, or at least about 8000 units of C1 esterase inhibitor.

10. The pharmaceutical system according to any of embodiments 1 to 9, wherein the C1 esterase inhibitor is a plasma-derived C1 esterase inhibitor.

11. The pharmaceutical system according to any of embodiments 1 to 10, wherein the C1 esterase inhibitor is a recombinant C1 esterase inhibitor, preferably a C1 esterase inhibitor having an amino acid sequence that is substantially identical to the amino acid sequence of human plasma-derived C1 esterase inhibitor.

12. The pharmaceutical system according to embodiment 11, wherein the recombinant esterase inhibitor is produced in a transgenic non-human mammal, selected from the group consisting of: a mouse, goat, bovine, sheep, porcine and an animal from the order *Lagomorpha,* such as a *Leporadae,* includinga rabbit.

13. The pharmaceutical system according to any of embodiments 9 to 12, wherein the C1 esterase inhibitor has a modified carbohydrate structure as compared to human plasma-derived C1 esterase inhibitor.

14. The pharmaceutical system according to any of embodiments 9 to 13, wherein the C1 esterase inhibitor has a reduced level of terminal sialic acid residues as compared to plasma derived C1 inhibitor, wherein said reduced level of terminal sialic acid residues results in a plasma half-life of less than 6 hours.

15. The pharmaceutical system according to any of embodiments 1 to 8, wherein another compound is used that has the same effect as a C1 esterase inhibitor such as an antibody to C1 esterase, an antibody to Kallikrein, a Kallikrein B1 or B2 receptor blocker or an antibody to F XII.

16. Use of a C1 esterase inhibitor as defined in embodiments 9 to 13 for the manufacture of a pharmaceutical system as defined in embodiment s 1 to 15.

17. A method of treatment of a subject suffering from or susceptible to a condition related to acute or chronic C1 esterase inhibitor deficiency, comprising administration of a pharmaceutical system according to any one of embodiment s 1 to 15 to the subject.

18. A method of treatment according to embodiment 17, wherein the condition related to acute or chronic C1 esterase inhibitor deficiency is hereditary angioedema (HAE).

19. A method of treatment according to embodiment 18, wherein the pharmaceutical system is a patch and wherein the patch is fixed to the skin of the subject.

20. A method of treatment according to embodiment 19, wherein subsequent to fixation, pressure is applied to the pharmaceutical patch.

21. A method of treatment according to embodiment 19 or 20, wherein the pharmaceutical patch is applied to the back, shoulder, nates, buttocks or back of the thigh of the subject, to allow the body weight of the subject to apply pressure to the pharmaceutical patch.

22. A method of treatment according to any one of embodiments 19 to 21, wherein the pharmaceutical patch is kept on the subject for at least about half an hour, about one hour, about two, hours, about three hours, about four hours, about five hours, at least about six hours, at least about eight hours, at least about ten hours, at least about twelve hours.

23. A method of treatment according to any one of embodiments 20 to 23, wherein about 25, about 50 or about 100 units C1 esterase inhibitor per kg bodyweight is transferred to the subject.

24 A method of treatment according to embodiment 18 or 19, wherein the pharmaceutical system is a microneedle system and wherein the microneedle system discharges the C1 esterase inhibitor load into the skin of the subject.

25. A method of treatment according to embodiment 24, wherein about 5, 10, 15, 20, 25, 50 or 100 units C1 esterase inhibitor per kg bodyweight or a total dose of about 2100 units of C1 esterase inhibitor is transferred to the subject.

The following examples are offered for illustrative purposes only and are not intended to limit the scope of the present invention in any way.

Examples

Example 1

To a human subject of 80 kg suffering from an acute attack of HAE, a pharmaceutical patch according to the invention with a surface area of 25 cm^2 comprising 2000 units C1 esterase inhibitor (corresponding to a dose of 25 units per kg bodyweight is administered on the back of the thigh. Subsequently, pressure is applied to the pharmaceutical patch by the subject sitting. Within four hours, a decrease of over 20 mm VAS score is achieved (the visual analog scale (VAS); Reidl MA, Ann Allergy Asthma Immunol 2013, 110(4):295-9), demonstrating the effectivity of the pharmaceutical patch according to the invention.

Example 2

To a human subject of 80 kg suffering from an acute attack of HAE, a pharmaceutical patch according to the invention with a surface area of 25 cm^2 comprising 4000 units C1 esterase

inhibitor (corresponding to a dose of 50 units per kg bodyweight is administered on the back of the thigh. Subsequently, pressure is applied to the pharmaceutical patch by the subject sitting. Within four hours, a decrease of over 20 mm VAS score is achieved (the visual analog scale (VAS); Reidl MA, Ann Allergy Asthma Immunol 2013, 110(4):295-9), demonstrating the effectivity of the pharmaceutical patch according to the invention.

Example 3

To a human subject of 80 kg suffering from an acute attack of HAE, a dose of 2100 units C1 esterase inhibitor comprised in 3 ml of reconstitution buffer is administered to the subject using a microneedle system according to the invention. Within four hours, a decrease of over 20 mm VAS score is achieved (the visual analog scale (VAS); Reidl MA, Ann Allergy Asthma Immunol 2013, 110(4):295-9), demonstrating the effectivity of the pharmaceutical system according to the invention.

Example 4

To a human subject of 80 kg suffering from an acute attack of HAE, a dose of 2100 units C1 esterase inhibitor comprised in 3 ml of reconstitution buffer is administered to the subject using a microneedle system according to the invention as defined in W02006055795, W02007002521 , WO201 3055638, WO201 3055641 and W02007002522. Within four hours, a decrease of over 20 mm VAS score is achieved (the visual analog scale (VAS); Reidl MA, Ann Allergy Asthma Immunol 2013, 110(4):295-9), demonstrating the effectivity of the pharmaceutical system according to the invention.

Example 5

To a human subject of 80 kg suffering from HAE, pharmaceutical patches according to the invention with a surface area of 25 cm2 comprising 4000 units rhC1 esterase inhibitor (corresponding to a dose of 50 units per kg bodyweight is administered on the back of the thigh twice a week over a period of three months. Subsequent to administration, pressure is applied to the pharmaceutical patch by the subject sitting. During the three months treatment period the incidence of acute HAE attacks is significantly reduced by more than 50% as compared to the period prior to the treatment demonstrating the effectivity of the pharmaceutical patch according to the invention.

Example 6

To a human subject of 80 kg suffering from HAE, doses of 2100 units C1 esterase inhibitor comprised in 3 ml of reconstitution buffer is administered to the subject using a microneedle system according to the invention as defined in W02006055795, W02007002521 , WO201 3055638, WO201 3055641 and W02007002522, twice a week over a period of three months. During the three months treatment period the incidence of acute HAE attacks is significantly reduced by more than 50% as compared to the period prior to the treatment

demonstrating the effectivity of the pharmaceutical patch according to the invention.

Example 7

Study Title:

A Phase 2 Multicenter, Randomized, Double-Blind, Placebo-Controlled, 3-Period Crossover Study to Evaluate the Efficacy and Safety of Recombinant Human C1 Inhibitor in the Prophylaxis of Angioedema Attacks in Patients with Hereditary Angioedema (HAE)

Study Phase: 2

Primary Objective:

To evaluate the efficacy and safety of recombinant human C1 inhibitor (rhC1 INH) applied intradermally in the prophylaxis of angioedema attacks in patients with HAE

Secondary Objective:

To evaluate the safety of recombinant human C1 inhibitor (rhC1 INH) applied intradermally in the prophylaxis of angioedema attacks in patients with HAE

To evaluate immunogenicity of rhCI INH in the prophylaxis of angioedema attacks in patients with HAE

Study Design:

Multicenter, randomized, double-blind, placebo-controlled, 3-period crossover study of rhCI INH in prophylaxis of angioedema attacks in patients with HAE.

Group Sequence	**Period 1 (4 weeks)**	**Period 2 (4 weeks)**
A	rhC1INH 50 U/kg[a] IV twice weekly	rhC1INH 1400 U in 2 ml ID once daily
D	rhC1INH 1400 U in 2 ml ID once daily	rhC1INH 50 U/kg[a] IV twice weekly

U: units; IV: intravenous; ID: intradermal

Note: During all treatment periods, patients may receive acute treatment for angioedema attacks.

[a] Patients ≥ 84 kg will receive 4200 units.

Blood samples for immunogenicity will be collected at Screening, prior to the first study drug administration in each treatment period, and at the final follow-up visit. Blood samples for C1INH concentrations will be collected at Screening, pre-injection and post injection (30

minutes) after the first and last (8th) administration of each treatment period. C1q levels will be evaluated at Screening.

Patients who experience angioedema attacks during the study may receive acute treatment consisting of open label treatment with rhC1 INH (50 units/kg up to a maximum of 4200 units, for patients ≥ 84 kg), which may be administered at the study center or administered by the patient or a caregiver in their home following appropriate training .

Study Population:

Thirty patients (both male or female), 13 years of age or older with a laboratory confirmed diagnosis of HAE due to C1INH deficiency, will be enrolled.

Efficacy Assessments:

The primary endpoint is the monthly HAE attack rate, defined as the number of HAE attacks during each treatment period normalized by the number of days the patient participated in that period.

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Claims

1. A pharmaceutical system for transdermal administration of a pharmacologically active compound having the effect of a C1 esterase inhibitor, comprising a surface layer and the pharmacologically active compound having the effect of a C1 esterase inhibitor, such as a C1 esterase inhibitor.

2. A pharmaceutical system according to claim 1 wherein the pharmaceutical system is a patch and further comprises an adhesive layer and a removable protective layer, wherein the adhesive layer is located between the surface layer and the removable protective layer.

3. A pharmaceutical patch according to claim 2, wherein at least a portion of the C1 esterase inhibitor is contained in the adhesive layer and/or in the surface layer.

4. A pharmaceutical patch according to claim 2 or 3, further comprising a back layer which is impermeable to the C1 esterase inhibitor.

5. The pharmaceutical system according to any one of claims 2 to 4, further comprising microneedles, in case of a patch, the microneedles are on the surface layer optionally comprising a reservoir system operably linked to the microneedles comprising at least a part of the C1 esterase inhibitor.

6. The pharmaceutical patch according to claim 5, wherein the microneedles are hollow, solid, dissolving and/or hydrogel forming microneedles.

7. The pharmaceutical system according to any one of claims 1 to 74 or 5, wherein the pharmaceutical system is a microneedle patch as defined in WO20151 17938 or WO2016162449 or wherein the pharmaceutical system is a microneedle device as defined in WO201 6 118459, W02006055795, W02007002521 , W02007002522, WO2012122162, WO2013055638, WO20 13055641 or W02010059605.

8. The pharmaceutical system according to any of claims 1 to 7, wherein the surface layer of the patch has a surface area of at least 5, 10, 15, 20, 25, 30, 35, 40, 45, 50,. 55, 60, 65, 70, 75, 80, 85, 90, 95 or 100 cm^2.

9. The pharmaceutical system according to any of claims 1 to 8, comprising at least about 100, about 200, about 300, about 400, about 500, about 600, about 700, about 800, about 900, about 1000, about 1100, about 1200, about 1300, about 1400, about 1500, about 1600, about 1700, about 1800, about 1900, about 2000, about 2100, about 2200, about 2300, about 2400,

about 2500, about 3000, about 3500, about 4000, about 4500, about 5000, about 5500, about 6000, about 6500, about 7000, about 7500, or at least about 8000 units of C1 esterase inhibitor.

10. The pharmaceutical system according to any of claims 1 to 9, wherein the C1 esterase inhibitor is a plasma-derived C1 esterase inhibitor.

11. The pharmaceutical system according to any of claims 1 to 10, wherein the C1 esterase inhibitor is a recombinant C1 esterase inhibitor, preferably a C1 esterase inhibitor having an amino acid sequence that is substantially identical to the amino acid sequence of human plasma-derived C1 esterase inhibitor.

12. The pharmaceutical system according to claim 11, wherein the recombinant esterase inhibitor is produced in a transgenic non-human mammal, selected from the group consisting of: a mouse, goat, bovine, sheep, porcine and an animal from the order *Lagomorpha,* such as a *Leporadae,* includinga rabbit.

13. The pharmaceutical system according to any of claims 9 to 12, wherein the C1 esterase inhibitor has a modified carbohydrate structure as compared to human plasma-derived C1 esterase inhibitor.

14. The pharmaceutical system according to any of claims 9 to 13, wherein the C1 esterase inhibitor has a reduced level of terminal sialic acid residues as compared to plasma derived C1 inhibitor, wherein said reduced level of terminal sialic acid residues results in a plasma half-life of less than 6 hours.

15. The pharmaceutical system according to any of claims 1 to 8, wherein another compound is used that has the same effect as a C1 esterase inhibitor such as an antibody to C1 esterase, an antibody to Kallikrein, a Kallikrein B1 or B2 receptor blocker or an antibody to F XII.

16. Use of a C1 esterase inhibitor as defined in claims 9 to 13 for the manufacture of a pharmaceutical system as defined in claims 1 to 15.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/055030

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K38/05 A61K9/70 A61K35/16
ADD.

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 practicable, search terms used)
EPO-Internal , WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2017/176798 A1 (SHIRE HUMAN GENETIC THERAPIES [US]) 12 October 2017 (2017-10-12) cited in the application paragraphs [0135], [0213], [0221] - [0223]; claims 1, 6,24	1-16
X	WO 2016/160926 A1 (DYAX CORP [US]) 6 October 2016 (2016-10-06) page 41; examples 1- 3	1-16
X	WO 2014/207199 A1 (CSL BEHRING GMBH [DE]) 31 December 2014 (2014-12-31) page 47, lines 8-15; examples 1-4 page 44, line 4 - page 45, line 4 page 43, line 24 - page 45, line 4	1-16

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[X] Further documents are listed in the continuation of Box C.

[X] 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

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2019	04/04/2019

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Form PCT/ISA/210 (second sheet) (April 2005)

International application No
PCT/EP2019/055030

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

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International application No
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Information on patent family members

International application No

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