HU000028492T2

(19) **HU**

(11) Lajstromszám: **E 028 492**

(13) **T2**

MAGYARORSZÁG
Szellemi Tulajdon Nemzeti Hivatala

EURÓPAI SZABADALOM
SZÖVEGÉNEK FORDÍTÁSA

(21) Magyar ügyszám: **E 13 727040**
(22) A bejelentés napja: **2013. 04. 16.**

(96) Az európai bejelentés bejelentési száma:
EP 20130727040
(97) Az európai bejelentés közzétételi adatai:
EP 2822537 A1 **2013. 11. 21.**
(97) Az európai szabadalom megadásának meghirdetési adatai:
EP 2822537 B1 **2015. 12. 09.**

(51) Int. Cl.: ***A61K 9/00*** *(2006.01)*
A61K 31/00 *(2006.01)*
A61K 311/64 *(2006.01)*
A61K 3141/74 *(2006.01)*
A61K 315/05 *(2006.01)*
A61K 317/28 *(2006.01)*
A61P 11/02 *(2006.01)*

(86) A nemzetközi (PCT) bejelentési szám:
PCT/EP 13/001117
(87) A nemzetközi közzétételi szám:
WO 13170921

(30) Elsőbbségi adatok:
102012009495 **2012. 05. 14.** **DE**
102012011447 **2012. 05. 15.** **DE**

(72) Feltaláló(k):
GREVE, Harald, 40545 Düsseldorf (DE)

(73) Jogosult(ak):
Maria Clementine Martin Klosterfrau Vertriebsgesellschaft mbH, 50670 Köln (DE)

(74) Képviselő:
PINTZ ÉS TÁRSAI, Szabadalmi, Védjegy és Jogi Iroda Kft., Budapest

(54) **Kombinációs terápiás szer nátha kezelésére**

EP2822537

COMBINATION THERAPY AGENT FOR TREATING RHINITIS

DESCRIPTION

The present invention relates to the field of the treatment of rhinitis.

The present invention relates to a combination therapeutic agent in the form of a pharmaceutical composition for use in the topical treatment of nasal rhinitis for purposes of reducing the systemic absorption of imidazoline-based alpha-sympathomimetic substances.

By rhinitis (sometimes synonymously referred to as nasal catarrh or coryza) is understood to mean in the context of the present invention, in particular an acute or chronic inflammation of the nasal mucosa, wherein the rhinitis have a particularly infectious, allergic or pseudo-allergic origin. Rhinitis most often occurs as part of so-called colds or flu-like infections.

In addition to a differentiation of acute rhinitis and chronic rhinitis on the other hand, there is also a distinction among the various forms of rhinitis, for example, *Rhinitis acuta*, *Rhinitis atrophicans*, *Rhinitis allergica*, *Rhinitis hypertrophica*, *Rhinitis medicamentosa*, *Rhinitis pseudomembranacea*, *Rhinitis sicca* and *Rhinitis vasomotorica*.

In the so-called acute rhinitis (*Rhinitis acuta*), i.e. the common cold, it is usually a generally innocuous infection of the nasal mucosa and thus an infectious rhinitis, which may be triggered through a variety of viruses (especially rhinoviruses and/or adenoviruses); the main characteristic of acute rhinitis is a so-called runny nose and nasal congestion by swelling of the mucous membranes.

Overall, more than 200 "cold viruses" are known as a possible trigger of a viral rhinitis that can typically occur in the context of a common cold. In the context of a cold, which generally starts with a rhinitis, the *Rhinitis acuta* generally disappears. Occasionally however, it may sometimes become chronic, which, *inter alia*, is often accompanied by an increase in the volume of the mucous membranes in the region of the nasal turbinates leading to nasal obstruction.

For further details concerning rhinitis, reference may be particularly made to Pschyrembel, Medizinisches Wörterbuch, 257th edition, pages 1331/1332, in particular under the keywords: *"Rhinitis"*, *"Rhinitis allergica"*, *"Rhinitis atrophicans"*, *"Rhinitis hyperplastica"*, *"Rhinitis pseudomembranacea"*, *"Rhinitis sicca"* and *"Rhinitis vasomotorica"*.

Thus, since there are a variety of different types of viruses that can trigger rhinitis, and a variety of causes for the occurrence of rhinitis, rhinitis, particularly acute rhinitis, may not be generally causally treated, but only symptomatically, preferably topically, mostly by using sympathomimetic drugs (also referred to synonymously as so-called "deconstrictors" or "decongestants"), preferably alpha-sympathomimetic substances, such as xylometazoline and oxymetazoline or their physiologically tolerable salts.

Due to their vasoconstrictor properties, sympathomimetic substances lead to a reduction of the nasal mucosa swelling and decreased blood flow to the nasal vessels by local or topical application in the nose. Sympathomimetic substances usually act by direct or indirect binding to the adrenergic receptors, especially the alpha-adrenergic receptors. In the case of sympathomimetic substances based on imidazoline derivatives, in particular xylometazoline or oxymetazoline, direct-acting sympathomimetic substances, they cause smooth muscle contraction. Overall, there are numerous market products which contain sympathomimetic substances, especially xylometazoline or oxymetazoline or their physiologically tolerable salts, in particular their hydrochlorides, and are used as a decongestant to treat rhinitis (e.g. Olynth®, Nasensprayratiopharm®, Nasivin® etc.).

The problem with the use of sympathomimetic substances of the aforementioned type is, however, – in addition to a drying and swelling of the mucous membranes – their systemic absorption in the body (despite purely topical or local administration) as a result of passage through the mucous membranes. This can lead to serious side effects, as the vasoconstrictor effect is not restricted to the nasal vessels. Thus excessive systemic absorption of sympathomimetic substances in the body may cause headaches, insomnia,

fatigue, blurred vision and allergic reactions. Moreover, excessive systemic absorption of sympathomimetic substances, especially xylometazoline or oxymetazoline, leading to vasoconstriction may have a serious impact on the cardiovascular system because of reduced blood flow that must be compensated; among other things, it can lead to a general increase in blood pressure and lead to a tachycardia. It is also disadvantageous when sympathomimetic substances are systemically spread to the extremities, i.e. distant from the trunk and the thus less perfused parts of the body, such as fingers, toes, chin and hands, and there cause vasoconstriction in the already naturally low perfused body regions.

Consequently, sympathomimetic substances of the aforementioned type may be administered topically only in extremely small doses in order to avoid a systemic absorption in appreciable quantities, since - as previously explained – even in the case of topical or intranasal administration of the sympathomimetic substance, there also always occurs a certain systemic absorption due to the passage through the nasal mucosa. Consequently, the required amounts for optimal therapeutic effect may not always be applied.

The internet publication *Open Drug Data Base / drugs / technical information (http://ch.oddb.org/de/gcc/fachinfo/reg/56839)* relates to the self-administrable market product "Nasic®", which is used to reduce the swelling of the nasal mucosa in episodically occurring runny nose (*Rhinitis vasomotorica*) and for the treatment of nasal obstruction as used after surgery on the nose. This composition is based firstly on xylometazuline and secondly on dexpanthenol.

WO 2010/015253 A1 discloses a composition particularly for the prophylactic or curative treatment of dry nasal mucous membranes or of rhinitis, wherein the composition or combination contains, in respectively pharmaceutically effective amounts, ectoine or at least an ectoine derivative on the one hand, and pantothenol or at least a pantothenol derivative or pantothenic acid on the other, as well as their physiologically acceptable salts. Moreover, the composition may also contain a sympathomimetic substance.

Furthermore, WO 03/049747 A1 relates to a pharmaceutical composition comprising pantholenol or pantothenic acid and hyaluronic acid or hyaluronate, as well as, optionally, additional pharmaceutical excipients.

Moreover, EP 0773022 A2, which refers to the applicant himself, discloses a pharmaceutical composition for the treatment of acute rhinitis, which, in combination and in a physiological concentration, contains, on the one hand, a suitable sympathomimetic substance with a 2-imidazoline structure for topical application, as well as pantothenol pantothenic acid on the other.

What equally concerns the applicant himself, in fact, is DE 20 2012 022 792 U1 that was published subsequently and thus does not have any priority claim to prior art as this document relates to a pharmaceutical composition for topical nasal administration for the treatment of rhinitis, wherein the stability of the composition is increased by the use of specific buffer systems and the adjustment of a specific pH value.

Therefore, the underlying problem for the present invention is to provide a suitable composition, in particular a pharmaceutical composition for topical, particularly nasal, preferably intranasal, administration, particularly for the treatment of rhinitis, which at least substantially avoids the above described disadvantages of the prior art, or at least mitigates them, in particular with respect to a lower systemic absorption of sympathomimetic substances, especially oxymetazoline or xylometazoline when used for topical or local application.

To solve the problem outlined above, the present invention proposes - in accordance with a first aspect of the present invention - a combination therapeutic agent in the form of a pharmaceutical composition for use in topical nasal treatment of rhinitis in order to reduce the systemic absorption of imidazoline-based alpha-sympathomimetic substances according to claim 1; further, particularly advantageous embodiments of the inventive therapeutic combination are the subject of the relevant dependent claims.

According to a second aspect of the present invention, the present invention relates to pantothenol for use in the prophylactic or curative treatment of rhinitis in accordance with the relevant independent claim.

It is to be understood in the subsequent explanations that the configurations, embodiments, advantages and the like, are set forth below in such a way as to avoid repetitions and only relate to one aspect of the invention while, of course, also applying accordingly to the other aspects of the invention, without a separate mention being needed.

In all the relative or percentage weight-related information listed below, in particular quantities, it remains to be noted that these are to be so selected by a person skilled in the art in the context of the present invention that the sum involving all the components or ingredients, in particular as defined below, always adds up to 100% or 100 wt.-%; this is automatically understood by a person skilled in the art.

Incidentally, a person skilled in the art may vary the weight, volume and range specifications given below for the application or the individual case without leaving the scope of the present invention.

In addition, all the value or parameter information referred to in the following, may be generally calculated or determined by the person skilled in the art using standardised or explicitly indicated methods of determination or otherwise, that lead *per se* to the common destination or measurement methods.

Having said that, the present invention is described in detail below.

The present invention is thus - according to a **first** aspect of the present invention - a combination therapeutic agent in the form of a pharmaceutical composition for use in the topical treatment of rhinitis to reduce the systemic absorption of imidazoline-based alpha-sympathomimetic substances,

wherein the pharmaceutical composition contains in combination, and in each case in pharmaceutically effective amounts:

(a) (a1) pantothenol (dexpanthenol) or its physiologically acceptable esters and/or

(a2) pantothenic acid or its physiologically acceptable salts; and

(b) at least one imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salt.

In other words, the object of the present invention is the use of (a) (a1) pantothenol (dexpanthenol) or its physiologically acceptable esters and of (a2) pantothenic acid or its physiologically acceptable salts for the reduction of the systemic absorption of imidazoline-based alpha-sympathomimetic substances for the topical nasal, preferably intranasal, application of at least an imidazoline-based alpha-sympathomimetic substance for the treatment of rhinitis or for the manufacture of a drug for the treatment of rhinitis, wherein the (a) (a1) pantothenol (dexpanthenol) or its physiologically acceptable esters and/or (a2) pantothenic acid or its physiologically acceptable salts, is administered together with and/or in combination with (b) the imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salts.

According to the invention, it is therefore provided that (a) (a1) the pantothenol (dexpanthenol) or its physiologically acceptable esters and/or (a2) the pantothenic acid or its physiologically acceptable salts is prepared for administration together with and/or in combination with (b) the imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salts.

In the present invention, it was completely surprising that the additional use of pantothenol (dexpanthenol) and/or pantothenic acid can significantly reduce the systemic absorption of sympathomimetic substances, especially imidazoline-based sympathomimetic substances, in the bloodstream upon topical, especially nasal, preferably intranasal, application in the context of treatment of rhinitis. In addition, it was surprising that the topical efficacy of the sympathomimetic substance, i.e. in relation to its vasoconstriction or decongestant effect on the nasal mucosa, is not affected even with the use of the inventively provided and relatively large amounts of pantothenic acid or pantothenol. Previously it was only known that pantothenol or pantothenic acid in common nasal or intranasal administration with sympathomimetic substances, especially imidazoline-based sympathomimetic substances, only resulted in desiccation of the nasal mucosa as a result of administration of the sympathomimetic substance.

In other words, in the context of the present invention, pantothenol or pantothenic acid is used in a completely novel way, namely to significantly reduce an undesirable systemic absorption of sympathomimetic substances in the bloodstream, especially imidazoline-based sympathomimetic substances, through topical or local (e.g. intranasal) application, resulting in a novel optimisation of the quantitative ratios of the components used, and offers a new approach with a novel mode of action.

Thus, as the applicant has surprisingly found in the context of clinical trials, the combined use of pantothenol or pantothenic acid along with sympathomimetic substances such as, for example, xylometazoline and/or oxymetazoline or their salts, through local or topical (especially intranasal) application of sympathomimetic substances leads to the prevention, or a significant reduction, in the systemic absorption of the administered sympathomimetic substance, which, may always be otherwise observed as a result of the passage through the nasal mucosa; by special adjustment of the ratios, systemic absorption of topically applied sympathomimetic substances may, therefore, be effectively prevented or at least limited.

The advantage of a reduced systemic absorption of sympathomimetic substances is, in particular, that a vasoconstrictor effect is not extended to the cardiovascular system, while side effects such as hypertension, tachycardia or hypoperfusion of peripheral parts of the body can be avoided.

As also performed by the applicant, and shown in detail below in the reference embodiments, the aforementioned effects on the purpose-driven and optimised use of pantothenol or pantothenic acid in combination with sympathomimetic substances, especially imidazoline-based sympathomimetic substances, through the nasal, preferably intranasal application, in the treatment of rhinitis, in particular in this context, it is already noted at this point that the embodiments of the applicant demonstrate the above effect in an impressive way.

Preferred embodiments of the present invention are set forth hereinafter for a better understanding.

With respect to the component (a), this is typically selected from pantothenol (dexpanthenol) or its physiologically acceptable esters, and is preferably pantothenol (dexpanthenol).

It has proved to be particularly advantageous, according to the invention, to select the component (b) or the imidazoline-based alpha-sympathomimetic substance from xylometazoline or oxymetazoline, in particular in the form of their physiologically acceptable salts, and particularly preferably in the form of their hydrochloride salts.

According to a particularly preferred embodiment, the component (b) or the imidazoline-based alpha-sympathomimetic substance xylometazoline, is, in particular, in the form of its physiologically acceptable salts, more preferably in form of its hydrochloride salt (xylometazoline hydrochloride).

According to the invention therefore, a combination of component (a) and component (b) is provided in order to prevent, or at least reduce, the systemic absorption of the component (b) through topical or local application.

In the present invention, it is preferable that (a) pantothenol (dexpanthenol) or its physiologically acceptable esters together with and/or in combination with (b) at least an imidazoline-based alpha-sympathomimetic substance are selected from the xylometazoline and/or oxymetazoline group or their physiologically acceptable salts, and are particularly preferably used and/or prepared for administration in the form of their hydrochloride salts.

In particular, it may be provided in the context of the present invention that (a) pantothenol (dexpanthenol) or its physiologically acceptable esters, preferably pantothenol (dexpanthenol), along with and/or in combination with (b) xylometazoline or its physiologically acceptable salts, is used and/or is prepared for administration more preferably in the form of its hydrochloride salt (xylometazoline hydrochloride). In the context of the present invention, it has in fact been shown that the absorption-reducing effect of pantothenol or pantothenic acid with respect to sympathomimetic substances especially occurs when used in combination with imidazoline-based sympathomimetic substances, preferably xylometazoline.

According to the invention, it is provided that the component (a) on the one hand and the component (b) on the other are present in a common pharmaceutical composition. It is inventively provided that the component (a) on the one hand and the component (b) on the other are present in a common composition, since this ensures a reliable joint application of both components (a) and (b).

In other words, it is provided in the context of the present invention that the aforementioned components (a) and (b) are present in an individual composition in the form of a combined preparation.

In connection with the application or administration of pantothenol or pantothenic acid, it is preferable according to the invention, if the component (a) is preferably administered in the form of pantothenol (dexpanthenol) with an individual dose in the range of 0.1 mg to 50 mg, particularly in the range of 0.5 mg to 25 mg, preferably in the range from 1 mg to 20 mg, more preferably in the range of 2.5 mg to 10 mg, particularly preferably in the range of 4 mg to 8 mg, or if the component (a) is preferably administered in the form of pantothenol (dexpanthenol), with an individual dose within the range of 0.1 mg to 50 mg, in particular in the range from 0.5 mg to 25 mg, preferably in the range from 1 mg to 20 mg, more preferably in the range of 2.5 mg to 10 mg, particularly preferably in the range of 4 mg to 8 mg. With respect to the individual doses mentioned above, according to the invention it is also common to administer 2 to 10 individual doses per day, in particular 3 to 5 individual doses per day, preferably spread over the day, or that the component (a), preferably in the form of pantothenol (dexpanthenol), is administered in 2 to 10 individual doses per day, in particular 3 to 5 individual doses per day, preferably spread over the day.

As regards the administration of sympathomimetic substances, it is preferred in the context of the present invention, if the component (b), preferably in the form of xylometazoline and/or oxymetazoline or their physiologically acceptable salts, more preferably in the form of xylometazoline hydochloride, is administered with an individual dose in the range of 0.001 mg to 10 mg, in particular in the range of 0.01 mg to 5 mg, preferably in the range of 0.05 mg to 2 mg, more preferably in the range of 0.08 mg to 1 mg, particularly preferably in the range of 0.1 mg to 0.8 mg, and if the component (b), preferably in the form of xylometazoline or oxymetazoline and/or their physiologically acceptable salts, in the form of xylometazoline hydochloride is administered with an individual dose within the range of 0.001 mg to 10 mg, particularly in the range of 0.01 mg to 5 mg, preferably in the range of 0.05 mg to 2 mg, more preferably in the range of 0.08 mg to 1 mg, particularly preferably in the range of 0.1 mg to 0.8 mg. In connection with the above-described individual dose of the sympathomimetic substance, it is provided in the context of the present invention that usually 2 to 10 individual doses per day, in particular 3 to 5 individual doses may be administered per day, preferably spread over the day, and that component (b) preferably in the form of xylometazoline and/or oxymetazoline, or their physiologically acceptable salts, more preferably xylometazoline hydochloride is administered in 2 to 10 individual doses per day, in particular 3 to 5 individual doses per day, preferably spread over the day.

For a sufficient affect on the one hand and a reduced or decreased systemic absorption of the sympathomimetic substance on the other, it has also been found according to the present invention that, in particular, the quantitative ratio of the component (a) to component (b) is of importance. in this connection it is preferred that the component (a) together with and/or in combination with the component (b) is used in a weight ratio of component (a) to component (b) from 10:1 to 1,000:1, in particular 15:1 to 500:1, preferably 20:1 to 250:1, preferably 25:1 to 200:1, more preferably 30:1 to 175:1, very particularly preferably 40:1 to 150:1, most preferably 45:1 to 125:, or if the component (a) together with and/or in combination with the component (b) is administered in a weight ratio of component (a) to component (b) in the range of 10:1 to 1000:1, especially 15:1 to 500:1, preferably 20:1 to 250:1, more preferably from 25:1 to 200:1, even more preferably 30:1 to 175 1, particularly preferably 40:1 to 150:1, most preferably 45:1 to 125:1.

The effectiveness and absorption reduction are ensured in the same manner through the above-mentioned amounts and proportions. Nevertheless, it is not excluded that a person skilled in the art in an individual case or related application can use different ranges of values to the above-mentioned without leaving the scope of the present invention.

The amount of component (a) may vary over a wide range within the scope of the present invention. In order to ensure sufficient effect of the component (a) in use, it is provided according to the invention that the component (a) is incorporated in the pharmaceutical composition or administered in the pharmaceutical composition, wherein the composition, based on the composition, contains the component (a) in an amount of 0.01 to 10 wt.-%, in particular 0.1 to 9 wt.-%, preferably 0.5 to 8 wt.-%, more preferably from 1 to 7 wt.-%, particularly preferably 2 to 6 wt.-%, most preferably 3 to 6 wt.-%.

If the aforementioned quantity ranges are significantly exceeded, then the nasal mucosa - without intending to be limited in this case to this theory – are so covered or overlaid with pantothenol or pantothenic acid that no bonding of the sympathomimetic substances, in particular the imidazoline-based sympathomimetic substances, may be effected at the target receptors, as the diffusion through the skin down to the receptors is not possible or only with difficulty. If the aforementioned quantities, however, fall below, no absorption-reducing effect can be ensured because - again without intending to be limited in this case to theory - the sympathomimetic substances may diffuse completely unhindered into the systemic bloodstream. In this context, this has already been taken into account in the embodiments according to the invention.

Similarly, the amount of component (b) may also vary within wide ranges. In the context of the present invention, it is provided that the component (b) is incorporated in the pharmaceutical composition or administered in the pharmaceutical composition, wherein the composition, based on the composition, contains component (b) in an amount of 0.001 to 2 wt.-%, in particular 0.005 to 1.5 wt.-%, preferably 0.01 to 1.2 wt.-%, more preferably 0.02 to 1.0 wt.-%, particularly preferably 0.03 to 0.5 wt .-%, most preferably 0.04 to 0.2 wt.%.

As already described above, component (a) and component (b) are generally in a common composition. According to the invention, component (a) and component (b) are applied starting from a common composition. In particular, dosing errors can be avoided in this way when both components are present in a common composition, as it can be ensured that component (a) and component (b) are always used in the optimal and inventively optimised quantity ratio. Thus, it is provided in the context of the present invention that the component (a) and the component (b) are incorporated in a common pharmaceutical composition or that the component (a) and the component (b) are administered in the common pharmaceutical composition.

Moreover, it is preferred in the context of the present invention, if the component (a) together with and/or in combination with the component (b) are used and/or administered in a (common) aqueous composition, and/or in a (common) aqueous composition. According to the invention, it can therefore be provided that the component (a) together with and/or in combination with the component (b) is prepared and/or administered in an aqueous system, particularly in the form of a (common) aqueous solution or (joint) aqueous solubilisation.

Preferably, the component (a) together with and/or in combination with the component (b) is prepared and/or administered as an aqueous system, in particular as an aqueous individual-phase system, preferably as an aqueous solution or aqueous solubilisation. In this context, it may be equally provided that the component (a) together with and/or in combination with the component (b) is prepared and/or administered with a water-based excipient or carrier. Moreover, it can be provided that the component (a) together with and/or in combination with the component (b) is prepared and/or administered as a clear, colourless aqueous solution.

In view of stabilisation of the components (a) and (b) in the solution or solubilisation, especially with respect to long term stability and storage stability, adherence to a very narrow pH regime in the range of 5.0 to 6.2 has proved to be particularly advantageous, especially without the use of additional stabilisers or preservatives. Thus it is particularly advantageous in the context of the present invention, if the component (a) together with and/or in combination with the component (b) in the pharmaceutical composition is prepared or administered with a pH value in the range of 5.0 to 6.2, in particular in the range of 5.0 to 6.0, preferably in the range of 5.1 to 6.0, more preferably in the range from 5.2 to 5.9. As the previous embodiments show, a particularly efficient stabilisation

between the two components (a) and (b) is thus achieved in particular by maintaining a slightly acidic pH. In particular, hydrolytic degradation of the components (a) and (b) is prevented by the aforesaid slightly acidic pH range, which results in particularly good storage stability.

According to the invention in the context of the present invention, the determination and measurement of the pH value is effected by a person skilled in the art through known or common or standardised methods, especially at 20 °C and atmospheric pressure (1013.25 mbar). As is known, the so-called pH is a dimensionless measurement which, according to DIN 19260: 1971-03 is defined as the negative logarithm of the hydrogen ion activity. In the present invention, the disclosure of pH refers in particular to the method of determination in accordance with DIN 19266: 2000-01, which has replaced the earlier DIN 19266: 1979-08. For further details regarding the term pH and its measurement and determination, reference can be made in particular to Römpp Lexikon Chemie, 10th edition, Georg Thieme Verlag, Stuttgart/New York, Volume 4, 1998, pages 3230 to 3232, Keyword: "*pH*", as well as the literature cited therein, wherein the entire aforementioned reference is incorporated herein by reference to the literature cited therein.

In connection with the stabilisation of the components (a) and (b) used, the kind of buffer system used is also important. Thus, it is within the scope of the present invention, if at least one chemical buffer system, especially buffer salt(s), is used for the adjustment and/or maintenance of the pH-value of the pharmaceutical composition. For the concept of chemical buffer or buffer systems, reference can be made especially to Römpp Lexikon Chemie, 10th edition, Georg Thieme Verlag, Stuttgart/New York, Volume 5, 1998, pages 3618/3619, Keyword: "*buffer*" as well as reference to the literature cited therein, wherein the relevant contents are hereby incorporated for reference.

In this context, a chemical buffer system may in particular be provided, preferably in the form of a dihydrogen phosphate/disodium phosphate buffer system ("$H_2PO_4^-/HPO_4^{2-}$ buffer (system)" or a "phosphate buffer (system)"), in particular an alkali dihydrogen phosphate/alkali disodium phosphate buffer system may be used.

It has proved particularly advantageous if the dihydrogen phosphate/disodium phosphate buffer system has a dihydrogen phosphate/disodium phosphate molar ratio greater than 5:1, in particular in the range from 5:1 to 110:1, more preferably in the range of 6:1 to 105:1, most preferably in the range from 7:1 to 100:1, or if the pharmaceutical composition, the dihydrogen phosphate/monohydrogen phosphate buffer system, has a dihydrogen phosphate/monohydrogen phosphate molar ratio greater than 5:1, in particular in the range of 5:1 to 110 :1, more preferably in the range of 6:1 to 105:1, most preferably in the range of 7:1 to 100:1. As described by the applicant, stability studies have shown that such a phosphate buffer system brings about reliable long-term stabilisation of the components (a) and (b) lasting several months and even years.

In view of a further stabilisation, or prevention of microbial growth, it may also be provided according to the invention that the administration of components (a) and (b) together with and/or in combination with (c) involves at least one preservative and/or disinfectant. Similarly, it may be provided that the components (a) and (b) together with and/or in combination with (c) are prepared for administration with at least a preservative and/or disinfectant. Moreover, the studies conducted by the applicant have surprisingly shown that the additional presence of a preservative or disinfectant, in particular based on benzalkonium chloride, effects a further reduction in the systemic absorption of locally or topically administered sympathomimetic substances; such an effect of the preservative or disinfectant additionally used was completely surprising and unpredicted.

In this context, it is usually provided that the components (a), (b) and (c) are incorporated or are present in the pharmaceutical composition in order to be administered in the common pharmaceutical composition.

As regards the use of a preservative or disinfectant as component (c) in particular, it is preferred in the context of the present invention if the preservative or disinfectant is selected from the group of (i) alkylbenzyldimethylammonium chlorides, in particular C_8-C_{16}-alkylbenzyldimethylammonium chlorides, and mixtures of various alkylbenzyldimethylammonium chlorides, preferably

benzalkonium chloride, (ii) para-hydroxybenzoic acid esters, and mixtures of various para-hydroxybenzoic acid esters, preferably from nipa-esters, (iii) chlorhexidine as well as combinations of the aforementioned compounds, and most preferably benzalkonium chloride. In the context of the present invention, the applicant has surprisingly found that the additional use of a preservative or disinfectant, in particular benzalkonium chloride, reinforces the effect of the components (a) and (b). In particular, the use of a preservative or disinfectant is associated with the advantage that, because of the disinfectant effect, the effect of the components (a) and (b) is supported and, in addition counteracts germ growth in an efficient manner both during storage and after application to the mucosa.

The amount of component (c) used, in particular benzalkonium chloride, is equally variable. In particular, it can be provided that the component (c), preferably in the form of benzalkonium chloride is administered with an individual dose range of 0.001 mg to 5 mg, in particular in the range of 0.005 mg to 2 mg, preferably in the range of 0.01 mg to 1 mg, or if the component (c) is prepared, preferably in the form of benzalkonium chloride, for administration with an individual dose within the range of 0.005 mg to 2 mg, preferably in the range of 0.01 mg to 1 mg; on the basis of, in particular from 2 to 10 individual doses per day, in more particularly from 3 to 5 individual doses per day, and preferably spread over the day. In other words, it may be provided, in particular, that the component (c), preferably in the form of benzalkonium chloride, is prepared for administration in 2 to 10 individual doses per day, in particular in 3 to 5 individual doses per day, preferably spread over the day.

In addition, it is usual in the context of the present invention that the component (c) is incorporated in the pharmaceutical composition or that the component (c) is administered in the pharmaceutical composition, wherein the composition, based on the composition, contains component (c) in an amount of 0.001 to 10 wt.-%, in particular 0.005 to 5 wt.-%, preferably 0.01 to 2 wt.-%, more preferably 0.01 to 1 wt.-%, particularly preferably 0.01 to 0.5 wt.-%. In this case, therefore, the composition preferably contains the components (a), (b) and (c).

In the context of the present invention, it is thus particularly advantageous if the components (a), (b) and (c) are incorporated or present in the common pharmaceutical composition and/or are administered in the common pharmaceutical composition.

Equally, as the applicant has surprisingly found, glycosaminoglycans, in particular hyaluronic acid and the salts thereof, can also support the effect of the other components, in particular the pantothenol or pantothenic acid. Moreover, the above-mentioned glycosaminoglycans, preferably hyaluronic acid, have a beneficial effect with respect to the relief of infection and inflammation of the nasal mucosa - probably due to their ability to bind large amounts of liquid – and, as a result, cause an acceleration of the regeneration of the inflamed tissue. In addition, the glycosaminoglycans, in particular hyaluronic acid and the salts thereof, together with the component (a), effect a further reduction or decrease of an undesired systemic absorption of topically or locally applied sympathomimetic substances.

In the context of the present invention, it has been found to be advantageous if the administration of the components (a) and (b) and optionally (c) is carried out together with and/or in combination with (d) at least one preferably acidic glycosaminoglycan or its physiologically acceptable salts or derivatives, in particular hyaluronic acid or its physiologically acceptable salts, or that the components (a) and (b) and optionally (c) are administered together with and/or in combination with (d) at least one preferably acidic glycosaminoglycan or its physiologically acceptable salts or derivatives, in particular hyaluronic acid or its physiologically acceptable salts. It is particularly advantageous if the components (a), (b), (c) and (d) are incorporated or administered in the common pharmaceutical composition and/or are present in the common pharmaceutical composition.

As regards the amounts used of the above-mentioned glycosaminoglycans, these may then vary within wide ranges. In particular, it can be provided in the context of the present invention that the component (d) is incorporated in the pharmaceutical composition

and/or the component (d) is administered in the pharmaceutical composition, wherein the composition, based on the composition, component (d) contains an amount of 0.0001 to 10 wt.-%, in particular 0.001 to 5 wt.-%, preferably 0.01 to 2 wt.-%.

In the context of the present invention, it may further be envisaged that the administration of the components (a) and (b) and optionally (c) and/or (d) is carried out together with and/or in combination with (e) ectoine or at least an ectoine derivative, in particular a hydroxyectoine, or that the components (a) and (b) and optionally (c) an or (d) are administered together with and/or in combination with (e) ectoine or at least an ectoine derivative, in particular a hydroxyectoine. In this connection it may in particular be provided that the components (a) and (b) and optionally (c) and/or optionally (d) and the component (e) are incorporated in the common pharmaceutical composition and/or are administered in a common pharmaceutical composition.

Because, as the applicant has surprisingly found, the use of ectoine or an ectoine derivative is advantageous in accelerating the regeneration of inflamed and/or sore nasal mucosa, as often occurs in the context of rhinitis. Ectoine or ectoine derivatives also support the reduction of the systemic absorption of the locally applied sympathomimetic substance.

The amount of ectoine used is variable within wide ranges. In the context of the present invention, it is usually provided that the component (e) is incorporated in the pharmaceutical composition and/or the component (e) is administered in the pharmaceutical composition, wherein the composition, based on the composition, contains component (e) in an amount of 0.0001 to 10 wt.-%, in particular 0.001 to 5 wt.-%, preferably 0.01 to 2 wt.-%.

Moreover, it can be provided in the context of the present invention that the administration of the components (a) and (b) and optionally (c), (d) and/or (e) takes place together with and/or in combination with (f) sodium chloride, or that the components (a) and (b) and optionally (c), (d) and/or (e) are prepared for administration together with and/or in combination with (f) sodium chloride. Also in this context, it is usual that components (a) and (b) and optionally (c), (d) and/or (e) and the component (f) are incorporated or are present in the common pharmaceutical composition and/or are administered in the common pharmaceutical composition. Sodium chloride, in particular, causes moistening of the nasal mucosa and thus also contributes to accelerated regeneration of inflamed nasal mucosa.

The amount of sodium chloride added may vary in wide ranges. In particular, it can be inventively provided that the component (f) is incorporated in the pharmaceutical composition and/or that the component (f) is administered in the pharmaceutical composition, wherein the composition, based on the composition, contains component (e) in an amount of 0.001 to 5 wt.-%, in particular 0.01 to 2 wt.-%, preferably 0.1 to 1 wt.-%.

Furthermore, it can be inventively provided that the component (a) is used or prepared for administration together with and/or in combination with the component (b) with at least one further ingredient. In this context it is particularly preferred if the additional ingredient is selected from the group of processing aids, stabilisers, emulsifiers, antioxidants, humectants, thickeners, antiseptics, colourants, flavourings, fragrances, perfumes, extenders, binders, wetting substances, vitamins, trace elements, minerals, micronutrients and/or essential oils and combinations thereof.

Moreover, it has been shown in the context of the present invention that good compatibility is ensured at the nasal mucosa by setting an osmolality in defined areas. The osmolality can - as the following embodiments show - vary in a wide range. According to the invention, it has proved to be advantageous if all active substances and/or ingredients, in particular the components (a) and (b) and optionally (c), (d), (e) and/or (f) are incorporated and/or administered in the common pharmaceutical composition, wherein the composition has an osmolality in the range of 300 to 600 mosm/kg, in particular in the range of 310 to 550 mosm/kg, preferably in the range from 300 to 525 mosm/kg, more preferably in the range of 325 to 510 mosm/kg, most preferably in the range of 350 to 500 mosm/kg.

In the context of the present invention, it is also preferred if all active substances and/or ingredients, especially components (a) and (b) and optionally (c), (d), (e) and/or (f) are incorporated and/or administered in the common pharmaceutical composition, wherein the composition at a temperature of 20 °C and at a pressure of 1013.25 mbar has a relative density, based on pure water, in the range of 1.001 to 1.2, in particular in the range of 1.005 to 1.15 preferably in the range from 1.005 to 1.105.

Moreover, the components used, particularly the components (a) and (b) remain stable in the context of the present invention under normal conditions over a very long period of time, in particular stable in storage. Thus, according to the invention, it is usual that all active substances and/or ingredients, in particular the components (a) and (b) and optionally (c), (d), (e) and/or (f) are incorporated or administered in the common pharmaceutical composition, wherein the composition at temperatures in the range from 20 °C to 50 °C, at a pressure of 1013.25 mbar and at a relative humidity in the range of 50% to 90%, can remain stable for at least 6 months, especially at least 12 months, preferably at least 24 months, more preferably at least 36 months, in particular stable in storage.

As the above embodiment shows in the context of the present invention, all active substances or ingredients, in particular the pantothenol or pantothenic acid and the imidazoline-based sympathomimetic substances, are thus distinguished by excellent stability and an extremely low content of degradation products.

In particular, even in long-term storage, degradation products of the components (a) or (b) only arise to an extremely minor extent: imidazoline-based sympathomimetic substances, such as xylometazoline or oxymetazoline are generally degraded by hydrolytic cleavage of the imidazole ring to form the corresponding amide. Such degradation products are referred to below as "impurity A". Thus, it is common within the scope of the present invention, for all active substances and/or ingredients, in particular the components (a) and (b) and optionally (c), (d), (e) and/or (f) to be incorporated and/or to be administered in the common pharmaceutical composition, wherein the composition has a content of degradation product(s) of component (b), in particular of impurity A, of at most 5 wt.-%, in particular not exceeding 3 wt.-%, preferably of at most 2 wt.-%, particularly preferably at most 1 wt.-%, based on the active ingredient (b) which allows, in particular, storage of the drug at temperatures ranging from 20 °C to 50 °C, at a pressure of 1013.25 mbar and at a relative humidity in the range of 50% to 90%, for at least 6 months, especially at least 12 months, preferably at least 24 months, more preferably at least 36 months.

In the case of degradation of the component (a) and pantothenic acid or pantothenol, however, aminopropanol and/or D-pantolactone is produced as a degradation product. Usually, it behaves in such a manner in the context of the present invention that all active substances and/or ingredients, in particular the components (a) and (b) and optionally (c), (d), (e) and/or (f) are incorporated and/or administered in the common pharmaceutical composition, wherein the composition has a content of degradation product(s) of the component (a), in particular aminopropanol and/or D-pantolactone, in each case of not more than 5 wt.-%, in particular in each case of not more than 3 wt.-%, preferably in each case of not more than 2 wt .-%, particularly preferably in each case of not more than 1 wt.-%, based on the active ingredient (a) which, in particular, even after storage of the drug at temperatures in the range of 20 °C to 50 °C, at a pressure of 1013.25 mbar and at a relative humidity in the range of 50% to 90%, can be stored for at least 6 months, especially at least 12 months, preferably at least 24 months, more preferably at least 36 months. The component (a) is thus characterised by its excellent stability.

In the context of the present invention, the composition is used in particular for the treatment of rhinitis of any kind described above, in particular *Rhinitis acuta*, *Rhinitis allergica*, *Rhinitis atrophicans*, *Rhinitis hyperplastica* or *hypertrophicans*, *Rhinitis mutilans*, *Rhinitis nervosa* or *vasomotorica* or *Rhinitis pseudomembranacea*, preferably *Rhinitis acuta*. In particular, however, a therapeutic combination of the present invention is suitable for a prophylactic and/or curative topical treatment of rhinitis, in particular *Rhinitis acuta*.

The administration of the compositions described in the present invention is carried out with the usual devices for topical, particularly nasal, administration. Thus it may be provided in the context of the present invention that all active substances and/or ingredients, in

particular the components (a) and (b) and optionally (c), (d), (e) and/or (f), are incorporated and/or administered in the common pharmaceutical composition, wherein the composition is administered and/or prepared for administration by means of an application device, preferably in the form of a container with a drop or spray device.

In order to apply a sufficient amount, it is preferable according to the invention that the application device is a spray device for the uniform application of the composition having an amount per puff in the range of 25 µl to 300 µl, and in particular in the range of 50 µl to 200 µl, preferably in the range of 75 µl to 125 µl.

Similarly, it is usually provided in this context that the application device comprises a reservoir having a volume in the range of 5 ml to 100 ml, particular from 10 ml to 50 ml.

As the above embodiments show in the context of the present invention, it is the first time that one has succeeded in providing an entirely novel concept of using pantothenol or pantothenic acid in the context of a reduction in the systemic absorption of imidazoline-based sympathomimetic substances, particularly xylometazoline. This novel concept allows the application of sufficient amounts of the sympathomimetic substance to achieve an excellent vasoconstrictor effect, while reducing the incidence of side effects, especially side effects related to the cardiovascular system resulting from the nasal, particularly intranasal, administration for the treatment of rhinitis of all types, by reducing the systemic absorption of sympathomimetic substances.

For further details concerning the therapeutic combination of the invention, reference can be made in the following embodiments to the further aspect of the invention, which applies correspondingly in relation to the therapeutic combination of the invention.

Furthermore, the present invention – according to a second aspect of the present invention – relates to pantothenol (dexpanthenol) or its physiologically acceptable esters and/or pantothenic acid or its physiologically acceptable salts for use in the prophylactic and/or curative treatment of rhinitis by nasal, preferably intranasal, administration for the purpose of reducing the systemic absorption of a imidazoline-based alpha-sympathomimetic substance, wherein the pantothenol (dexpanthenol) or its physiologically acceptable esters and/or the pantothenic acid or its physiologically acceptable salts is administered together with and/or in combination with the imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salts.

Similarly, the present invention relates to pantothenol (dexpanthenol) or its physiologically acceptable esters and/or pantothenic acid or its physiologically acceptable salts for use in the nasal, preferably intranasal, treatment of rhinitis together with and/or in combination with at least one imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salts for the purpose of reducing the systemic absorption of imidazoline-based alpha-sympathomimetic substances.

For further details concerning the second aspect of the present invention, reference can be made to the foregoing embodiments of the therapeutic combination agent according to the invention, which apply correspondingly in relation to the second aspect of the invention.

A method is also described here for the treatment of rhinitis by nasal, preferably intranasal, administration of at least one imidazoline-based alpha-sympathomimetic substance or its physiologically acceptable salts containing, in particular, a rhinologic substance, wherein to reduce the systemic absorption of the imidazoline-based alpha-sympathomimetic substance together with and/or in combination with the imidazoline-based alpha-sympathomimetic substance, at least one compound selected from the group consisting of pantothenol (dexpanthenol) or its physiologically acceptable esters and/or pantothenic acid or its physiologically acceptable salts is administered.

For further details of the method, reference may be made to the preceding embodiments for the other aspects of the invention, which apply correspondingly in relation to the method.

Thus, for the first time, in the context of the present invention, an efficient therapy concept or combination therapeutic agent has been provided for the reduction of systemic absorption of imidazoline-based sympathomimetic substances in their topical application. As

the applicant has surprisingly found, the combined administration of pantothenol (dexpanthenol) or pantothenic acid with sympathomimetic substances causes a significant reduction, if not prevention, of the systemic absorption of locally administered sympathomimetic substances. This was completely surprising and unpredictable. Thus, for the first time, a more optimised combination therapeutic agent is provided through the optimised adjustment of the amounts of active substances of the two aforementioned components (a) and (b), which allows for optimal administration of sympathomimetic substances in the treatment of rhinitis.

Further embodiments, modifications and variations as well as advantages of the present invention are readily discernible and realisable for a person skilled in the art upon reading the description without departing from the scope of the present invention.

The following exemplary embodiments are merely illustrative of the present invention, without the present invention being restricted thereto.

Examples

1. Preparation examples

General procedure

For the production of 1,000 g of a clear aqueous solution of the composition according to the present invention in a manner known to a person skilled in the art: first, at room temperature and ambient pressure, a defined amount of purified water (e.g. 300 ml to 600 ml) is stirred in an appropriate reaction vessel or glass vessel with a stirring device, and subsequently a solution of a buffer system based on potassium/sodium monohydrogen phosphate (dodecahydrate) with a predetermined pH is added, followed by controlling the adjusted pH value. The adjusted pH values vary in the range of values specified in the formulation examples. The amount of dexpanthenol specified in the formulation examples is then added and completely dissolved through thorough stirring. A preservative or disinfectant, preferably benzalkonium chloride, preferably in the form of an aqueous solution, is then optionally added and also dissolved through stirring. Subsequently, the desired amount of xylometazoline hydrochloride is added, and more water added to give the final weight of 1,000 g, and stirred until homogeneous. Optionally, the solution may be filtered through a neutral cellulose filter. Finally, the pH is checked again. The other specifications of the solution with respect to the adjusted or selected ranges are checked (e.g. osmolality: 350-395 mosm/kg; relative density at 20 °C: 1.01 to 1.05; microbiological purity and sterility; exclusion of impurities, especially degradation products of the components used). A portion of the resulting solution is finally filled in narrow mouth bottles made of brown glass of 10 ml or 20 ml, which can be optionally equipped with a drop or a spray dosing pump; to determine the correct application, 1 to 3 drops or 1 to 3 sprays of 75 to 125 µl can be given in each nostril and applied several times a day.

After this general preparation, the formulations specified below may be prepared in order to evaluate the impact of (a) the amount of dexpanthenol, (b) the influence of pH, and (c) the effect of preservatives.

a) Influence of the amounts of dexpanthenol used

In order to investigate the influence of the amount of dexpanthenol used, six compositions prepared according to the above-described instructions are provided, each of which contain 0 wt .-% (non-inventive, formulation A), 0.1 wt .-% (formulation B), 3.0 wt .-% (formulation C), 5.0 wt .-% (formulation D), 6.0 wt .-% (formulation E) and 9.0 wt .-% (formulation F) of dexpanthenol. Moreover, the compositions each contain 0.1 wt .-% xylometazoline hydrochloride and are each adjusted to a pH value in the range from 5.2 to 5.9, an osmolality in the range 350-395 mosm/kg, and a relative density at 20 °C in the range 1.005 to 1.105. The precise details regarding the foregoing compositions can be found in the tables below. The amounts indicated relate to 10g of the composition.

Non-inventive formulation A (without dexpanthenol) for comparison:

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	0	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9,902	Ph.Eur.

Inventive formulations:

Formulation B (0.1wt.-% dexpanthenol)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	10	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9,892	Ph.Eur.

Formulation C (3.0 wt.-% dexpanthenol)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	300	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9,602	Ph.Eur.

Formulation D (5.0 wt.-% dexpanthenol)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	500	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9,402	Ph.Eur.

Formulation E (6.0 wt% dexpanthenol)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	600	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9.302	Ph.Eur.

Formulation F (9.0 wt .-% dexpanthenol)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	900	Ph. Eur.
Buffer system Potassium dihydrogen phosphate/ sodium monohydrogen- phosphate (dodecahydrate)	89.30 2.70	Ph. Eur.
Purified water	9.002	Ph.Eur.

b) Effect of the pH value

In order to investigate the influence of pH on the effectiveness of the composition, two other compositions (formulations G and H) containing a combination of active ingredients are prepared on the basis of 5 wt .-% dexpanthenol and 0.1 wt .-% xylometazoline hydrochloride, with a osmolality in the range 350-395 mosm/kg, a density in the range 1.005 to 1.105, and a pH of 5.0 (formulation G) and 6.2 (formulation H). There is also a buffer system based on potassium dihydrogen phosphate/sodium monohydrogen phosphate (dodecahydrate). Apart from the pH values, the compositions thus correspond, in terms of their ingredients, to the composition at a 5.0 wt .-% of dexpanthenol amount (formulation D) already described above and to which reference is made to avoid unnecessary repetition.

c) Effect of the use of benzalkonium chloride

To investigate the influence of preservatives or disinfectants based on benzalkonium chloride, a composition is prepared which contains 5.0 wt .-% dexpanthenol, 0.1 wt .-% xylometazoline as well as 0.02 wt .-% benzalkonium chloride as a 50 % solution (formulation I). The pH of the composition is in the range of 5.2 to 5.9, the density in the range of 1.005 to 1.105 and the osmolality in the range of 350 to 395 mosm/kg. The formulation of the composition is shown in the following table.

Formulation I (0.02 wt .-% benzalkonium chloride)

Ingredient	Amount/mg	Quality
Xylometazoline hydrochloride	10.00	Ph. Eur.
Dexpanthenol	500	Ph. Eur.
Buffer system	89.30	Ph. Eur.

Potassium dihydrogen phosphate/ sodium monohydrogen-phosphate (dodecahydrate)	2.70	
Preservative/disinfectant substance: benzalkonium chloride (50% solution)	4.00	Ph.Eur.
Purified water	9.002	Ph.Eur.

2. Application observations:

To check the validity of the test compositions, each of 12 subjects from a group of 108 patient volunteers aged 20 to 73 years (66 male, 42 female) who suffered from acute rhinitis, were each treated with one of the formulations A to I described in Section 1.) for the duration of the disease (generally 3-7 days); the formulations were applied topically several times a day as a spray. A good vasoconstrictor effect, i.e. a satisfactory swelling of the nasal mucosa, could generally be achieved with all the compositions employed.

Particularly good results with respect to the decongestant effect on the one hand as well as the prevention of desiccation of the nasal mucosa on the other, were achieved with the compositions according to the invention B, D, E, and G.

In the case of the subjects, who had been tested with the inventive composition formulation A, a stronger drying of the nasal mucosa was observed due to the lack of the effect of dexpanthenol according to the invention.

In the case of the subjects, who had been tested with the inventive composition formulation F, which contained dexpanthenol in an amount of 9 wt.-%, a slightly reduced vasoconstrictor effect was observed compared to the other composition. Nevertheless, the effectiveness was assessed overall as good.

3. Clinical study analysing the absorption of xylometazoline:

In the context of an open, 2-way crossover, placebo-controlled, randomised individual dose study, the systemic absorption of xylometazoline after topical intranasal application in the presence or absence of dexpanthenol was investigated.

In this context, a group of subjects with 108 people with ages between 18 to 55, of which 52 were female, and male, was used. The body mass index (BMI) of the subjects ranged from 19 and 28 kg/m². The subjects were prescribed to be in a good health condition. As part of the clinical study, the 108 subjects were divided into 9 subgroups of 12 subjects who each received one of the compositions described above for analysis. The procedure in the context of the clinical trial is described below.

As previously mentioned, the experiments were carried out in an open, block-randomised, 2-way crossover, placebo-controlled individual dose study with two periods and two sequences. The subjects were examined at a time point 24 hours after application of the composition to be tested or monitored clinically. The procedure in the context of the study was that the subjects in the context of the first period of the clinical trial at the time point 0 were given an individual dose of the test composition (i.e. a spray puff of 75 to 125 µl each per nostril). Before application of the composition (time point 0), two blood samples of 5 ml and 20 ml were taken from the subjects. At time points 5 min, 10 min, 15 min and 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 5.0, 6, 0, 8.0, 12.0 and 24.0 hours after administration of the respective test composition, blood samples of 5 ml were taken from each subject for analysis. The elution time from the application date was five days. This was followed by the second period, wherein an individual dose of each composition was re-administered. Blood sampling was performed as in the first period. Overall, two application periods were performed with each subject group. In the blood samples, the concentration of xylometazoline was determined by HPLC-MS/MS. In addition, the pharmacokinetic parameters of the maximal systemic concentration of xylometazoline (C_{max}) in the blood, as well as the pharmacokinetic parameter AUC_{0-t} were determined, which represents the area under the integrated concentration curve of

xylometazoline in the plasma between the time t_0 and the last analysed sample (t_{last}). The results are shown in the table below, where low values of the parameters C_{max} and AUC_{0-t} are an indicator of a desired, reduced systemic absorption of xylometazoline according to the invention:

Table: Results of the clinical trial with respect to the systemic absorption of xylometazoline (hydrochloride form)

Form.	A	B	C	D	E	F	G	H	I
C_{max} [pg/ml]	62.7	60.3	59.9	56.4	55.4	52.2	57.3	56.9	55.2
AUC_{0-t}	629.3	580.2	490.0	424.5	422.1	419.3	426.3	427.2	420.9

For statistical evaluation of C_{max} and AUC_{0-t}, a logarithmic transformation of the measured values was initially performed. Subsequently, the aforementioned pharmacokinetic parameters were determined by variance analysis.

The foregoing results in terms of measured and statistically evaluated amounts of xylometazoline in the blood, i.e. with respect to the systemic absorption of xylometazoline, show that systemically absorbed amounts of xylometazoline can be significantly lowered by the targeted use of dexpanthenol in defined amounts.

In this context, a dexpanthenol amount of 5.0 wt .-% (formulation D) has proven to be optimal. In the case of the use of 5.0 wt .-% dexpanthenol compared with the non-inventive use of 0 wt .-% dexpanthenol (formulation A), 33% less xylometazoline, based on the total amount of xylometazoline was absorbed in the blood measured in the sample period. Moreover, the maximum xylometazoline concentration of 5 wt .-% of dexpanthenol is more than 10% below the maximum xylometazoline concentration without the use of dexpanthenol. By the use of dexpanthenol in an amount of 5 wt .-%, the effectiveness of the xylometazoline, i.e. the vasoconstrictor effect, is not impaired, as is also shown in particular by the results in section 2.).

With the use of only 0.1 wt .-% dexpanthenol (formulation B), the amount of systemically absorbed xylometazoline in the blood increases, however, it is still much lower than without the use of dexpanthenol.

The use of 9.0 wt .-% dexpanthenol (formulation F) only leads to a slight decrease in the systemic absorption of xylometazoline system compared to the use of 5.0 wt .-% or 6.0 wt .-% dexpanthenol, except that the vasoconstrictor effect of xylometazoline through the use of dexpanthenol in an amount of 9.0 wt .-%, is easily influenced (see results in Section 2.)).

Taking into account all relevant factors – i.e. efficacy on the one hand and reduction of absorption on the other - dexpanthenol amounts ranging from 3.0 wt .-% to 6.0 wt .-% appear to be optimal.

Moreover, a pH value in the range of 5.2 to 5.9 has proven to be optimal. However, as the results in connection with the formulations G and H show, good results are achieved even with a pH value lower or higher than 5.0 or 6.2.

Through the use of benzalkonium chloride as a preservative or disinfectant (formulation I), the properties of the compositions can be still further improved for the intranasal administration, as is apparent from the above results.

Overall, the above-referenced results show that dexpanthenol has a significant completely surprisingly effect on the systemic absorption of xylometazoline on intranasal administration. In the context of the present invention, therefore, a novel approach has been found in a surprising manner, which leads to a limitation or alleviation of the serious side effects of xylometazoline. Furthermore, the pharmaceutical effect, i.e. the vasoconstrictor effect of xylometazoline or alpha-sympathomimetic substances, is not particularly affected by the additional use of dexpanthenol in the ranges of amounts selected for the relief of systemic application.

EP2822537

KOMBINÁCIÓS TERÁPIÁS SZER NÁTHA KEZELÉSÉRE

SZABADALMI IGÉNYPONTOK

1. Kombinációs terápiás szer gyógyászati kompozíció formájában, nátha (orrnyálkahártya-gyulladás) (nasal rhinitis) helyi kezelésében való felhasználásra imidazolin-alapú alfa-szimpatomimetikus anyagok szisztémás abszorpciójának csökkentése céljából, ahol a gyógyászati kompozíció tartalmaz kombinációban és gyógyászatilag hatékony mennyiségekben

(a1) pantotenolt (dexpantenolt) vagy ennek fiziológiailag elfogadható észtereit és/vagy

(a2) pantoténsavat vagy ennek fiziológiailag elfogadható sóit; és

legalább egy imidazolin-alapú alfa-szimpatomimetikus anyagot vagy annak fiziológiailag elfogadható sóit.

2. Az 1. igénypont szerinti kombinációs terápiás szer és annak 1. igénypont szerinti alkalmazása, ahol az (a) összetevőt a következők közül választhatjuk ki: pantotenol (dexpantenol), vagy ennek fiziológiailag elfogadható észterei, és az összetevő előnyösen pantotenol (dexpantenol); és/vagy

ahol a (b) összetevőt és/vagy az imidazolin-alapú alfa-szimpatomimetikus anyagot a következők közül választhatjuk ki: xilometazolin és oximetazolin, előnyösen ezek fiziológiailag elfogadható sói formájában, különösen előnyösen ezek hidroklorid sói formájában; és/vagy

ahol a (b) összetevő és/vagy az imidazolin-alapú alfa-szimpatomimetikus anyag a következők közül választható ki: xilometazolin, előnyösen ennek fiziológiailag elfogadható sói formájában, különösen előnyösen ennek hidroklorid sója (xilometazolin hidroklorid) formájában.

3. Az 1. vagy 2. igénypont szerinti kombinációs terápiás szer és ennek 1. vagy 2. igénypont szerinti alkalmazása,

ahol az (a) összetevő előnyösen pantotenol (dexpantenol) formájában van bevezetve olyan egyedi (single) dózisokkal, amelyek a 0,1 mg és 50 mg közötti tartományban, elsősorban a 0,5 mg és 25 mg közötti tartományban, előnyösen az 1 mg és 20 mg közötti tartományban, előnyösebben a 2,5 mg és 10 mg közötti tartományban, különösen előnyösen a 4 mg és 8 mg közötti tartományban vannak, vagy ahol az (a) összetevő előnyösen pantotenol (dexpantenol) formájában van bevezetve olyan egyedi dózisokkal, amelyek a 0,1 mg és 50 mg közötti tartományban, elsősorban a 0,5 mg és 25 mg közötti tartományban, előnyösen az 1 mg és 20 mg közötti tartományban, előnyösebben a 2,5 mg és 10 mg közötti tartományban, különösen előnyösen a 4 mg és 8 mg közötti tartományban vannak, különösen ahol 2-10 egyedi (individual) dózis lehet bevezetve naponta, elsősorban 3-5 egyedi dózis naponta, előnyösen elosztva az egész napon keresztül, és/vagy különösen az (a) összetevő előnyösen pantotenol (dexpantenol) formájában van bevezetve 2-10 egyedi (individual) dózisban naponta, elsősorban 3-5 egyedi dózisban naponta, előnyösen elosztva az egész napon keresztül, és/vagy

ahol a (b) összetevő előnyösen xilometazolin és/vagy oximetazolin vagy gyógyászatilag elfogadható sóik, előnyösebben xilometazolin hidroklorid formájában van bevezetve olyan egyedi dózisokkal, amelyek a 0,001 mg és 10 mg közötti tartományban, elsősorban a 0,01 mg és 5 mg közötti tartományban, előnyösen a 0,05 mg és 2 mg közötti tartományban, előnyösebben a 0,08 mg és 1 mg közötti tartományban, különösen előnyösen a 0,1 mg és 0,8 mg közötti tartományban vannak, és ahol a (b) összetevő előnyösen xilometazolin és/vagy oximetazolin vagy fiziológiailag elfogadható sóik, előnyösebben xilometazolin hidroklorid formájában van bevezetve egy egységdózissal, amely a 0,001 mg és 10 mg közötti tartományban, elsősorban a 0,01 mg és 5 mg közötti tartományban, előnyösen a 0,05 mg és 2 mg közötti tartományban, előnyösebben a 0,08 mg és 1 mg közötti tartományban, különösen előnyösen a 0,1 mg és 0,8 mg közötti tartományban van, különösen ahol 2-10 egyedi (individual) dózis lehet bevezetve naponta, elsősorban 3-5 egyedi dózis naponta, előnyösen elosztva az egész napon

keresztül, és/vagy különösen ahol a (b) összetevő előnyösen xilometazolin és/vagy oximetazolin vagy fiziológiailag elfogadható sók formájában, előnyösen xilometazolin hidroklorid formájában van bevezetve előnyösen 2-10 egyedi dózisban naponta, különösen 3-6 egyedi dózisban naponta, előnyösebben az egész napon keresztül elosztva; és/vagy

ahol az (a) összetevő együtt és/vagy kombinációban a (b) összetevővel olyan tömegrészt képvisel, vagyis az (a) összetevő a (b) összetevőhöz olyan tömegarányt mutat, amely 10:1 és 1000:1 között, elsősorban 15:1 és 500:1 és között, előnyösen 20:1 és 250:1 között, előnyösebben 25:1 és 200:1 között, még előnyösebben 30:1 és 175:1 között, különösen előnyösen 40:1 és 150:1 között, még ennél is előnyösebben 45:1 és 125:1 között van, és/vagy ahol az (a) összetevő együtt és/vagy kombinációban a (b) összetevővel olyan tömegarányban van bevezetve az (a) összetevő és a (b) összetevő között, amely 10:1 és 1000:1 között, elsősorban 15:1 és 500:1 között, előnyösen 20:1 és 250:1 között, előnyösebben 25:1 és 200:1 között, még előnyösebben 30:1 és 175:1 között, különösen előnyösen 40:1 és 150:1 között, még ennél is előnyösebben 45:1 és 125:1 között van

4. Az 1-3. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-3. igénypontok bármelyike szerinti alkalmazás,

ahol az (a) összetevő be van építve a gyógyászati kompozícióba,

ahol a kompozícióra alapozva a kompozíció tartalmaz (a) összetevőt 0,01-10 tömeg %, elsősorban 0,1-9 tömeg %, előnyösen 0,5-8 tömeg %, előnyösebben 1-7 tömeg %, különösen előnyösen 2-6 tömeg %, és legelőnyösebben 3-6 tömeg % mennyiségben; és/vagy

ahol a (b) összetevő be van építve a gyógyászati kompozícióba, ahol a kompozícióra alapozva a kompozíció tartalmaz (b) összetevőt 0,001-2 tömeg %, elsősorban 0,05-1,5 tömeg %, előnyösen 0,01-1,2 tömeg %, előnyösebben 0,02-1,0 tömeg %, különösen előnyösen 0,03-0,5 tömeg %, legelőnyösebben 0,04-0,2 tömeg % mennyiségben; és/vagy

ahol az (a) összetevő együtt a (b) összetevővel és/vagy ezzel kombinációban vizes rendszerként van alkalmazva, elsősorban vizes egyfázisú rendszerként, előnyösen vizes oldatként vagy vizes szolubilizátumként van alkalmazva, és/vagy ez bevezetéshez van elkészítve, és/vagy ahol az (a) összetevő együtt a (b) összetevővel és/vagy ezzel kombinációban egy víz-alapú kötőanyaggal vagy hordozóval van alkalmazva és/vagy bevezetéshez elkészítve, és/vagy ahol az (a) összetevő együtt a (b) összetevővel és/vagy ezzel kombinációban tiszta, szintelen vizes oldatként van alkalmazva, és/vagy bevezetéshez van elkészítve..

5. Az 1-4. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-4. igénypontok bármelyike szerinti alkalmazás,

ahol az (a) összetevő együtt a (b) összetevővel és/vagy ezzel kombinációban van alkalmazva és/vagy bevezetéshez elkészítve a gyógyászati kompozícióban, olyan pH értéknél, amely az 5,0 és 6,2 közötti tartományban, elsősorban az 5,0 és 6,0 közötti tartományban, előnyösen az 5,1 és 6,0 közötti tartományban, előnyösebben az 5,2 és 5,9 közötti tartományban van;

különösen ahol a gyógyászati kompozíció pH értékének beállítása és fenntartása legalább egy kémiai puffer rendszert alkalmaz, előnyösen puffer só(ka)t, ahol előnyösen egy dihidrogén-foszfát/dinátrium-foszfát puffer rendszer [„$H_2PO_4^-$/HPO_4^{2-}- puffer (rendszer)" és „foszfát puffer (rendszer)"] van felhasználva, ahol elsősorban egy alkáli-dihidrogén-foszfát/alkáli-monohidrogén-foszfát puffer rendszer van felhasználva kémiai puffer rendszerként, és ahol elsősorban dihidrogén-foszfát/monohidrogén-foszfát puffer rendszer van felhasználva, a dihidrogén-foszfát/dinátrium-foszfát mólarány a nagyobb, mint 5:1-től indul, és különösen az 5:1 és 110:1 közötti tartományban, előnyösen a 6:1 és 105:1 közötti tartományban, és legelőnyösebben a 7:1 és 100:1 közötti tartományban van.

6. Az 1-5. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-5. igénypontok bármelyike szerinti alkalmazás,

ahol a bevezetéshez az (a) és (b) összetevők együtt vagy kombinációban (c)-vel, vagyis legalább egy konzerválószerrel (preserving agent) és/vagy fertőtlenítőszerrel (disinfecting agent) vannak elkészítve, különösen amikor az (a), (b) és (c) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban vagy egy gyógyszerben;

különösen ahol a konzerválószer és/vagy fertőtlenítőszer a következők közül választható ki: (i) alkil-benzil-dimetil-ammónium-kloridok, elsősorban C_8-C_{18}-alkil-benzil-dimetil-ammónium-kloridok, és különböző alkil-benzil-dimetil-ammónium-kloridok keverékei, előnyösen benzalkónium-klorid, (ii) para-hidroxi-benzoesav és különböző para-hidroxi-benzoesav észterek, előnyösen Nipa észterek, keverékei, (iii) klórhexidin, valamint az előzőekben említett vegyületek és legelőnyösebben benzalkónium-klorid kombinációi; és/vagy ahol a (c) összetevő előnyösen benzalkónium-klorid formájában van bevezetve olyan egyedi (single) dózisban, amely 0,001 mg és 5 mg közötti tartományban, elsősorban a 0,005 mg és 2 mg közötti tartományban, előnyösen a 0,01 mg és 1 mg közötti tartományban van, vagy ahol a (c) összetevő előnyösen benzalkónium-klorid formájában van bevezetve olyan egységdózisban (unit dose), amely a 0,005 mg és 2 mg közötti tartományban, előnyösen a 0,01 mg és 1 mg közötti tartományban van, és be lehet vezetve elsősorban 2-10 egyéni (individual) dózisban naponta, elsősorban 3-5 egyéni dózisban naponta, előnyösen az egész napon keresztül elosztva, és/vagy különösen ahol a (c) összetevő be van építve a gyógyászati kompozícióba, ahol ez 0,001 és 10 tömeg % közötti, elsősorban 0,005 és 5 tömeg % közötti, előnyösen 0,01 és 2 tömeg % közötti, előnyösebben 0,01 és 1 tömeg % közötti, és különösen előnyösen 0,01 és 0,5 tömeg % közötti mennyiségben tartalmaz (c) összetevőt.

7. Az 1-6. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-6. igénypontok bármelyike szerinti alkalmazás,
ahol az (a) és (b) és kívánt esetben (c) összetevők a bevezetéshez együtt vannak elkészítve és/vagy kombinációban (d)-vel, amely legalább egy, előnyösen savas glikózaminoglikán vagy fiziológiailag elfogadható sói vagy származékai, előnyösen hialuronsav vagy fiziológiailag elfogadható sói, ahol az (a), (b), (c) és (d) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban;
különösen ahol a (d) összetevő be van építve a gyógyászati kompozícióba, ahol a kompozíció, a kompozícióra alapozva, a (d) összetevőt 0,0001 és 10 tömeg % közötti, elsősorban 0,001 és 5 tömeg % közötti, előnyösen 0,01 és 2 tömeg % közötti mennyiségben tartalmazza.

8. Az 1-7. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-7. igénypontok bármelyike szerinti alkalmazás,
ahol az (a) és (b) és kívánt esetben (c) és/vagy (d) összetevők a bevezetéshez együtt vannak elkészítve és/vagy kombinációban (e)-vel, amely ektoin vagy legalább egy ektoin származék, elsősorban hidroxi-ektoin, ahol az (a), (b), (c), (d) és (e) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban;
különösen ahol az (e) összetevő be van építve a gyógyászati kompozícióba, ahol a kompozíció, a kompozícióra alapozva, az (e) összetevőt 0,0001 és 10 tömeg % közötti, elsősorban 0,001 és 5 tömeg % közötti, előnyösen 0,01 és 2 tömeg % közötti mennyiségben tartalmazza.

9. Az 1-8. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-8. igénypontok bármelyike szerinti alkalmazás,
ahol az (a) és (b) és kívánt esetben (c), (d) és/vagy (e) összetevők a bevezetéshez együtt vannak elkészítve és/vagy kombinációban (f)-el, amely nátrium-klorid, különösen ahol az (a), (b), (c), (d), (e) és (f) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban;
különösen ahol az (f) összetevő be van építve a gyógyászati kompozícióba, ahol a kompozíció, a kompozícióra alapozva, az (f) összetevőt 0,001 és 5 tömeg % közötti, elsősorban 0,01 és 2 tömeg % közötti, előnyösen 0,1 és 1 tömeg % közötti mennyiségben tartalmazza.

10. Az 1-9. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-9. igénypontok bármelyike szerinti alkalmazás,
ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők, be vannak építve vagy jelen vannak a gyógyászati kompozícióban, ahol az említett kompozíció ozmolalitási értéket

tartalmaz a 300 mosm/kg és 600 mosm/kg közötti tartományban, elsősorban a 310 mosm/kg és 550 mosm/kg közötti tartományban, előnyösen a 300 mosm/kg és 525 mosm/kg közötti tartományban, előnyösebben a 325 mosm/kg és 510 mosm/kg közötti tartományban, és legelőnyösebben a 360 mosm/kg és 500 mosm/kg közötti tartományban.

11. Az 1-10. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-10. igénypontok bármelyike szerinti alkalmazás, ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban, ahol a kompozíció 20°C hőmérsékletnél és 1013,25 mbar nyomásnál, tiszta vízre alapozva, olyan relatív sűrűséggel bír, amely az 1,001 és 1,2 közötti tartományban, elsősorban az 1,005 és 1,15 közötti tartományban, előnyösen az 1,005 és 1,105 közötti tartományban van; és/vagy
ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők, be vannak építve vagy jelen vannak a gyógyászati kompozícióban, ahol a kompozíció stabil, különösen stabil a tárolásnál olyan hőmérséklet-tartományban, amely 20°C és 50°C között van, 1013,25 mbar nyomásnál, és olyan relatív nedvességtartalomnál, amely az 50% és 90% közötti tartományban van, legalább 6 hónapig, elsősorban legalább 12 hónapig, előnyösen legalább 24 hónapig, előnyösebben legalább 36 hónapig.

12. Az 1-11. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-11. igénypontok bármelyike szerinti alkalmazás, ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban, ahol az említett kompozíció rendelkezik olyan tartalommal, amely a (b) összetevő bomlási termékét vagy termékeit képviseli, elsősorban az A szennyezést (impurity), legfeljebb 5 tömeg %-ban, amely elsősorban nem haladja meg a 3 tömeg %-ot, előnyösen legfeljebb 2 tömeg %, különösen előnyösen legfeljebb 1 tömeg %, a (b) aktív anyagra alapozva, amely elsősorban tárolás után van olyan hőmérséklet-tartományban, amely 20°C és 50°C között van, 1013,25 mbar nyomásnál, és olyan relatív nedvességtartalomnál, amely az 50% és 90% közötti tartományban van, legalább 6 hónapig, elsősorban legalább 12 hónapig, előnyösen legalább 24 hónapig, előnyösebben legalább 36 hónapig,
ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők be vannak építve vagy jelen vannak a gyógyászati kompozícióban, ahol az említett kompozíció rendelkezik olyan tartalommal, amely az (a) összetevő bomlási termékét vagy termékeit képviseli, elsősorban amino-propanolt és/vagy D-pantolaktont, nem több, mint 5 tömeg %-ban, elsősorban legfeljebb 3 tömeg %-ban, előnyösen legfeljebb 2 tömeg %-ban, különösen előnyösen legfeljebb 1 tömeg %-ban, az (a) aktív anyagra alapozva, amely elsősorban tárolás után van olyan hőmérséklet-tartományban, amely 20°C és 50°C között van, 1013,25 mbar nyomásnál, és olyan relatív nedvességtartalomnál, amely az 50% és 90% közötti tartományban van, legalább 6 hónapig, elsősorban legalább 12 hónapig, előnyösen legalább 24 hónapig, előnyösebben legalább 36 hónapig.

13. Az 1-12. igénypontok bármelyike szerinti kombinációs terápiás szer minden típusú nátha (orrnyálkahártya-gyulladás) (rhinitis) kezelésében való felhasználásra, elsősorban a következők kezelésében: Rhinitis acuta, Rhinitis allergica, Rhinitis atrophicans, Rhinitis hyperplastica vagy hypertrophicans, Rhinitis mutilans, Rhinitis nervosa vagy vasomotorica vagy Rhinitis pseudomembranacea, előnyösen Rhinitis acuta; és/vagy felhasználásra nátha, elsősorban Rhinitis acuta, megelőző és/vagy gyógyító helyi kezelésében.

14. Az 1-13. igénypontok bármelyike szerinti kombinációs terápiás szer és az 1-13. igénypontok bármelyike szerinti alkalmazás, ahol az összes aktív anyag és/vagy alkotórész, elsősorban az (a) és (b) összetevők és kívánt esetben a (c), (d), (e) és (f) összetevők be vannak építve a gyógyászati kompozícióba, ahol a kompozíció előnyösen egy alkalmazó készülék (application

device) segítségével van bevezetve tartály formájában csepegtetés (dripping) vagy permetezés (spraying) révén, és/vagy ez a bevezetéshez úgy van elkészítve a kompozíció egyenletes bevezetése érdekében, különösen ahol az alkalmazó készülék permetező (spraying) készülék, hogy a bevezetésenkénti (shot) mennyiség a 25 µl és 300 µl közötti tartományban, elsősorban az 50 µl és 200 µl közötti tartományban, előnyösen az 75 µl és 125 µl közötti tartományban legyen; és/vagy
ahol az alkalmazó készülék (application device) rendelkezik egy olyan tartállyal (reservoir), amelynek térfogata 5 ml és 100 ml közötti tartományban, előnyösen 10 ml és 50 ml közötti tartományban van.

15. Pantotenol (dexpantenol) vagy fiziológiailag elfogadható észterei és/vagy pantoténsav vagy fiziológiailag elfogadható sói alkalmazásra nátha (rhinitis) megelőző és/vagy gyógyító kezelésében orron keresztüli (nasal) bevezetés révén, imidazol-alapú alfa-szimpatomimetikus anyag szisztémás abszorpciójának csökkentése céljából, ahol a pantotenol (dexpantenol) vagy fiziológiailag elfogadható észterei és/vagy pantoténsav és fiziológiailag elfogadható sói együtt és/vagy kombinációban vannak bevezetve az imidazol-alapú alfa-szimpatomimetikus anyaggal vagy fiziológiailag elfogadható sóival.