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(54) Titre : COMPOSITION AQUEUSE IONIQUE CONTENANT DU LEVOMENTHOL
(54) Title: IONIC AQUEOUS COMPOSITION CONTAINING LEVOMENTHOL

(57) **Abrégé/Abstract:**

The invention concerns a composition in the form of an aqueous solution, in particular designed for relieving the sensation of breathing difficulties and/or promote the natural regeneration of the nose cavity mucous membrane. The invention is characterised in that it essentially consists of a levomenthol solution in an ionic aqueous solution having an osmolarity not less than that of a sodium chloride aqueous solution at 9 g/l and in which the levomenthol is dissolved, said ionic aqueous solution being selected from the group consisting of pure or diluted sea water and sodium chloride aqueous solutions optionally further containing at least one salt naturally present in sea water, the levomenthol having a concentration ranging between 10 and 250 mg/l. Said composition enables to improve the feeling of freshness provided by the levomenthol at the nose cavity cold receptors.



INTERNATIONAL PATENT APPLICATION

Title : IONIC AQUEOUS COMPOSITION CONTAINING LEVOMENTHOL

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ABSTRACT

The invention concerns a composition in the form of an aqueous solution, in particular designed for relieving the sensation of breathing difficulties and/or promote the natural regeneration of the nose cavity mucous membrane. The invention is characterised in that it essentially consists of a levomenthol solution in an ionic aqueous solution having an osmolarity not less than that of a sodium chloride aqueous solution at 9 g/l and in which the levomenthol is dissolved, said ionic aqueous solution being selected from the group consisting of pure or diluted sea water and sodium chloride aqueous solutions optionally further containing at least one salt naturally present in sea water, the levomenthol having a concentration ranging between 10 and 250 mg/l. Said composition enables to improve the feeling of freshness provided by the levomenthol at the nose cavity cold receptors.

IONIC AQUEOUS COMPOSITION CONTAINING LEVOMENTHOL

The present invention relates to an ionic aqueous composition containing levomenthol.

5 The nasal cavity contains sensitive receptors which are stimulated by the passage of air. When external modifications intervene, such as infestation by rhinovirus, variations in temperature or in atmospheric pressure for example, the mucous membranes of the nasal cavity react and get congested, and this creates a feeling of a blocked nose. This benign
10 affectation, which is commonly called the cold, normally gets better spontaneously but sometimes does lead, over several days, to a sensation of respiratory discomfort and a secretory malfunctioning of the nasal mucous membranes, which can give rise to a significant discomfort under numerous circumstances such as at work or for sleeping suitably, for example.

15 Several treatments are currently proposed. Via the general route or via the local route, these are medicaments which have a vasoconstrictory action. Their long term use can however cause local or general side-effects which are linked to their pharmacological action, which can be serious, such as an atrophy of the nasal mucous membranes or cardiovascular or prostate
20 troubles. Another treatment consists in the local administration of essential oils and/or of terpenic aromatic derivatives. Their local decongestant or antiseptic action, often claimed, is not however scientifically proved, and their use, alone or in combination, can prove to be dangerous for health by risking causing local irritations with the essential oils, or central nervous system
25 troubles, such as convulsions in the infant with camphor, for example. The risk is increased when these preparations contain alcohol, even in low proportions, or antiseptic substances, used for preventing microbial contamination but which can be irritants to the nasal mucous membranes. Infants, young children or elderly subjects are more particularly exposed to all
30 these risks.

 Natural menthol is a secondary alcohol of essence of mint which contains levomenthol but also menthone. Synthetic menthol or *d/l* menthol is an alcohol which is obtained by various synthetic methods, but *l*-menthol or levomenthol, which is the most active isomer for aromatisation, can also be
35 isolated or synthesised (*cf.* Codex 1965 - DORVAULT L'OFFICINE, Vigot, 23rd

ed. p.1055 (1995) - MARTINDALE, THE EXTRA PHARMACOPOEIA, The Pharmaceutical Press, 30th ed. p. 1386 (1993)).

It has already been proposed to use menthol, even levomenthol in compositions which are intended for decongesting the nasal mucous membranes.

5 However, menthol being known for its low solubility in aqueous solutions, various tricks are used for using it at concentrations higher than its limit of solubility in water, either by incorporating it in emulsions, or by introducing various organic products such as an oil or an alcohol to improve its dispersion.

10 The present invention results from a reverse process since the inventor has now discovered that it was possible to prepare particularly effective compositions by using levomenthol at a concentration which does not go over the limit of solubility of this latter compound, with the proviso of dissolving it in a sufficiently ionic aqueous medium, and more specifically a medium which is at least isotonic, and preferably even quite clearly
15 hypertonic.

 It will be recalled that in physiology, the term « isotonic » is qualified as a solution which exerts an osmotic pressure which is equal to that of normal blood plasma, e.g. physiological NaCl solute at 9 g per litre. A hypertonic solution means a solution which exerts an osmotic pressure which
20 is greater than that of normal blood plasma (example : NaCl solute the concentration of which is greater than 9g per litre). It is in this sense that it is necessary to understand the terms « isotonic » or « hypertonic ».

 As it emerges from the following description, insofar as solutions are covered here which optionally contain ions other than those which
25 constitute sodium chloride, their osmolarity will be referred to in order to define the osmotic behaviour of the ionic solutions of the invention.

 The osmolarity of a solution is designated as the concentration of the osmotically active particles, such as ions, in this solution. In physiology, solutions having an osmolarity equal to that of blood plasma are commonly
30 called « iso-osmotic » solutions. Those solutions having a higher osmolarity are called « hyperosmotic » solutions.

 More specifically, the invention relates to a novel composition in the form of an aqueous solution, notably intended for relieving the sensation of respiratory discomfort and/or for promoting the natural regeneration of
35 the mucous membranes of the nasal cavity. This solution is essentially

constituted of a levomenthol solution in an aqueous ionic solution having an osmolarity at least equal to that of an aqueous solution of sodium chloride at 9 g/l and in which the levomenthol is dissolved, said aqueous ionic solution being selected from the group constituted of pure or diluted sea water and aqueous sodium chloride solutions optionally further containing at least one salt naturally contained in sea water, the levomenthol being found at a concentration between 10 and 250 mg/l.

This composition has the double advantage of providing :

- 1) In the first place, an action of washing the nasal mucous membranes congested by a hypertonic or hyperosmotic ionic aqueous solution, or at least an isotonic or iso-osmotic solution. This washing action removes the mucus present on the congested mucous membranes and causes an osmotic effect, and this facilitates the natural regeneration of the mucous membranes of the nasal cavity. This aqueous ionic solution can be either pure or diluted sea water, or it can be water containing sodium chloride and, if need be, other salts naturally contained in sea water.

The concentration of sodium chloride, of the solution selected, is preferably equal to or greater than 9 grams per litre, a concentration which is called isotonic with blood or tears.

- 2) In second place, and additionally, an action on the heat-receptors or cold receptors of the mucous membranes of the nasal cavity. This action is obtained by the use of levomenthol, the only isomer of menthol being active on the heat-receptors or cold receptors, of the mucous membranes of the nasal cavity. Levomenthol acts on the flow of calcium ions through the cell membranes of these receptors. A refreshing effect is thus instantaneously felt and procures a sensation of ease of breathing which enables the sensation of respiratory discomfort due to the nasal congestion to be decreased, in anticipation of a natural regeneration of the mucous membranes of the nasal cavity and without the use of other substances or medicaments which might be dangerous.

Hence, the present invention gives a real synergy of the effects of its two constitutive elements, leading to a result which is particularly remarkable by its immediate effect.

In fact, the action of the levomenthol is optimised :

(i) by the washing, with an ionic solution, of the mucous membranes of the nasal cavity which has been ridded of mucus, and this renders the heat-receptors more easily accessible to the levomenthol, and

5 (ii) by the absence, in the composition, of combined substances, of the terpene or essential oil type or any other substance, which can decrease the access of the levomenthol to these heat-receptors.

The addition of a substance can be envisaged which is non-active upon the mucous membranes of the nasal cavity for, if need be, stabilising the pH of the composition.

10 As set forth above, it is important that the composition has an ion content which confers to it an osmotic pressure which is at least equal to that of an isotonic composition of sodium chloride.

On the contrary, too high a concentration of ions would risk leading to a composition which is too irritant for the nasal mucous
15 membranes.

This is the reason why the ionic compositions of the invention advantageously have an osmolarity which is equivalent to that of a solution of sodium chloride between 9 and 30 g/l, preferably between 12 and 18 g/l.

According to a preferred variant of the invention, the ionic
20 solution is pure or diluted sea water having an osmolarity as defined above.

According to another variant, the sea water will be replaced with a solution called « synthetic sea water », which contains sodium chloride and optionally other salts which are naturally contained in natural sea water.

All these solutions, whether it be natural sea water or synthetic sea
25 water, will contain a total content of ions such that they have an osmolarity as defined above.

Copper, zinc, iodine, magnesium, manganese, fluorine, selenium ions, as well as the ions found in trace state in sea water such as nickel, silver or cobalt ions, will be cited as examples amongst the ions introduced in the
30 form of salts in synthetic sea water.

These ions will be introduced for example in one of the following forms :

- copper sulphate,
- zinc chloride,
- 35 - potassium iodide,

- magnesium sulphate,
- manganese chloride,
- sodium fluoride,
- selenium chloride,

5 The various ions introduced will preferably be introduced at concentrations which are equal to or less than those usually encountered in sea water, or which are compatible with the standards in force of drinkability of drinking waters, or of acceptability for the composition of mineral waters.

10 The levomenthol is found in the compositions of the invention at contents at which it is in solution, and this without it being necessary to add products intended for improving its solubility or its dispersability. This constitutes an essential difference with the compositions of the prior art.

15 To that end, the concentration of the levomenthol in the compositions of the invention is advantageously between 30 and 200 mg/l, preferably between 100 and 180 mg/l.

20 The two constituents, the aqueous ionic solution and the levomenthol, are called essential constituents of the composition of the present invention in the sense that it is to their presence alone that the activity of the composition is linked. The presence of oil or alcohol, with the view notably to increasing the limit of solubility of the levomenthol in the composition is excluded. Such a presence could further more be harmful.

 However, it will be possible to admit the presence of a buffer intended for adjusting the pH to values between 6 and 12, preferably between 8 and 10, in the composition.

25 Those which are well tolerated by the mucous membranes of the nasal cavity and which can maintain the solution in slightly alkaline medium, *e.g.* sodium phosphate- or sodium bicarbonate-based buffer solutions, will be cited as examples of acceptable buffer solutions.

30 An advantage of the compositions of the invention is that, due to their simplicity, they can be prepared very economically, by simple mixing and agitation of their constituents. This mixing can then be followed by a filtering step, optionally by a sterilisation step.

35 Another advantage of the compositions of the invention is that they do not necessitate the addition of an antiseptic or of an additional preservative ; and this further decreases any risk of irritant character.

The classical steps of sterilisation and disinfecting notably by heat means or by irradiation do prove to be entirely sufficient for obtaining perfectly reliable compositions.

5 The composition of the invention has the advantage of being able to be manufactured industrially in an aseptic and sterile manner, and, without undergoing external microbial contamination which could reveal to be dangerous for the user.

The composition of the present invention is advantageously presented in a suitable device for nasal pulverisation or nebulisation.

10 As an example, an empty device can be filled with the composition which will beforehand have undergone a sterilising filtration. The device will then be closed or crimped in a way as to affix thereon the valve or the device which will ensure the pulverisation or the nebulisation. The whole of these operations can take place in an aseptic or sterile medium.

15 It may prove to be useful to pulverise or to nebulise micro-doses of these compositions, so as to repeat these operations several times per day in order to ensure the well-being of the user without risk to health.

According to another of its essential characteristics, the invention relates to the use of a composition in the form of a solution containing from
20 10 to 250 mg/l of levomenthol in aqueous solution in pure or diluted sea water or in an aqueous solution containing sodium chloride and optionally enriched with at least one ion naturally contained in sea water, said solution having an osmolarity corresponding to that of an aqueous solution of sodium chloride containing from 9 to 30 g/l, preferably 12 to 18 g of sodium chloride,
25 for preparing a composition intended for relieving the sensation of respiratory discomfort and/or for promoting the natural regeneration of the mucous membranes of the nasal cavity.

According to another of its essential characteristics, the invention relates to a method of treatment of colds, according to which the composition
30 as described above is administered by nasal pulverisation or nebulisation, so as to relieve the sensation of respiratory discomfort and/or to promote the natural regeneration of the mucous membranes of the nasal cavity.

According to another feature, the composition of the invention can be pulverised or nebulised, with the aid of a suitable device, into the
35 external auditory canal, with the view to cleaning this canal and to removing

impurities found therein and which, in accumulating, favour the formation of cerumen plugs.

According to another of its essential features, the invention relates to the use of optionally diluted sea water for obtaining an osmolarity which is equivalent to that of a solution of sodium chloride containing from 9 to 30 g/l, and preferably 12 to 18 g/l, or of a solution of sodium chloride optionally further containing at least one of the salts contained naturally in sea water and having an osmolarity which is equivalent to that of an aqueous solution of sodium chloride containing from 9 to 30 g per litre, preferably from 12 to 18 g of sodium chloride, as an agent intended for improving the sensation of freshness brought about by the levomenthol at the cold receptors of the nasal cavity.

All these compositions described above enable this effect of synergism to be observed between the two essential constituents of the composition and more particularly in the case of concentrations of levomenthol between 10 and 250 mg/l, preferably between 30 and 200 mg/l, more preferably between 100 and 180 mg/l.

The Examples which follow are given in a non-limiting way. The compositions which are described therein are obtained by mixing their constituents, filtering, sterilising, packing in a nebuliser or pulveriser flask, with or without propellant gas, or by any other method which enables the administration of the composition into the nasal cavity.

Example 1 :

	levomenthol	9 mg
25	sea water	50 ml

Example 2 :

	levomenthol	12 mg
	purified water	30 ml
30	sea water	70 ml

Example 3 :

	levomenthol	1 mg
35	sodium chloride	135 mg

	purified water	15 ml
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Example 4 :

	levomenthol	0,5 mg
5	sodium chloride	350 mg
	purified water	15 ml

Example 5 :

	levomenthol	15 mg
10	magnesium sulphate	5 mg
	sodium fluoride	4 mg
	selenium chloride	3 mg
	sodium chloride	1.2 mg
15	purified water	100 ml

Example 6 :

	levomenthol	12 mg
	copper sulphate	4 mg
	manganese chloride	2 mg
20	sodium chloride	1.4 mg
	purified water	100 ml

Example 7 :

	levomenthol	18 mg
25	zinc chloride	1.5 mg
	sodium chloride	1.8 mg
	purified water	100 ml

30 The compositions described in Examples 1 to 7 are administered in case of colds or in case of a blocked nose, at the rate of 1 to 10 nebulisations of 25 to 150 microlitres per day in each nostril.

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1. A composition in the form of an aqueous solution, for relieving the sensation of respiratory discomfort and/or for promoting the natural regeneration of the mucous membranes of the nasal cavity, said composition comprising

a levomenthol solution in an aqueous ionic solution having an osmolarity
5 at least equal to that of an aqueous solution of sodium chloride at 9 g/l and in which the levomenthol is dissolved,

wherein said aqueous ionic solution is pure sea water, diluted sea water or an aqueous sodium chloride solution optionally further containing at least one ion naturally contained in sea water, and

10 wherein the levomenthol is found at a concentration between 10 and 250 mg/l.

2. The composition according to claim 1, wherein said ionic solution has an osmolarity which is equivalent to that of a solution of sodium chloride containing from 9 to 30 g/l of sodium chloride.

15 3. The composition according to claim 1 or 2, wherein said ionic solution has an osmolarity which is equivalent to that of a solution of sodium chloride containing from 12 to 18 g/l of sodium chloride.

4. The composition according to any one of claims 1 to 3, wherein the aqueous ionic solution is pure or diluted sea water.

20 5. The composition according to any one of claims 1 to 3, wherein the aqueous ionic solution is the aqueous sodium chloride solution.

6. The composition according to any one of claims 1 to 3, wherein the aqueous ionic solution is the aqueous sodium chloride solution, further containing at least one ion naturally contained in sea water which is a copper, zinc, iodine, magnesium,
25 silver, manganese, fluorine, nickel, cobalt, or selenium ion.

7. The composition according to any one of claims 1 to 6, wherein the levomenthol is found at the concentration between 30 to 200 mg/l.

8. The composition according to any one of claims 1 to 7, wherein the levomenthol is found at the concentration between 100 to 180 mg/l.

9. The composition according to any one of claims 1 to 8, further comprising a buffer intended for adjusting the pH.

5 10. Use of a composition in the form of a solution, for preparing a composition intended for relieving the sensation of respiratory discomfort and/or for promoting the natural regeneration of the mucous membranes of the nasal cavity, said composition comprising

 from 10 to 250 mg/l of levomenthol in solution in an aqueous ionic
10 solution, wherein said aqueous ionic solution is pure sea water, diluted sea water or an aqueous solution containing sodium chloride and optionally further containing at least one ion naturally contained in sea water,

 wherein said aqueous ionic solution has an osmolarity corresponding to that of an aqueous solution of sodium chloride containing from 9 to 30 g/l of sodium
15 chloride.

 11. Use of a composition in the form of a solution, for preparing a composition intended for cleaning the external auditory canal and for removing impurities found therein, said composition comprising

 from 10 to 250 mg/l of levomenthol in solution in an aqueous ionic
20 solution which is pure sea water, diluted sea water or an aqueous solution containing sodium chloride and optionally further containing at least one ion naturally contained in sea water,

 wherein said aqueous ionic solution has an osmolarity corresponding to that of an aqueous solution of sodium chloride containing from 9 to 30 g/l of sodium
25 chloride.

 12. The use according to claim 10 or 11, wherein said aqueous ionic solution has an osmolarity corresponding to that of an aqueous solution of sodium chloride containing from 12 to 18 g/l of sodium chloride.

13. The use according to any one of claims 10 to 12, wherein said ion is a copper, zinc, iodine, magnesium, silver, manganese, fluorine, nickel, cobalt, or selenium ion.

14. Use, for improving the sensation of freshness brought about by
5 levomenthol at the cold receptors of the nasal cavity, of a composition comprising said levomenthol at a concentration from 10 to 250 g/l and

- optionally diluted sea water having an osmolarity which is equivalent to that of a solution of sodium chloride containing from 9 to 30 g/l of sodium chloride, or
- a solution of sodium chloride optionally further containing at least
10 one ion contained naturally in sea water and having an osmolarity which is equivalent to that of an aqueous solution of sodium chloride containing from 9 to 30 g/l of sodium chloride.

15. The use according to claim 14, wherein said solution of sodium chloride optionally further containing at least one ion contained naturally in sea water has
15 an osmolarity which is equivalent to that of an aqueous solution of sodium chloride containing from 12 to 18 g/l of sodium chloride.

16. The use according to claim 14, wherein said optionally diluted sea water has an osmolarity which is equivalent to that of an aqueous solution of sodium chloride containing from 12 to 18 g/l of sodium chloride.

20 17. The use according to claim 14 or 15, wherein said ion is a copper, zinc, iodine, magnesium, silver, manganese, fluorine, nickel, cobalt, or selenium ion.

18. The use according to any one of claims 10 to 17, wherein said levomenthol is found at the concentration between 30 to 200 mg/l.

19. The use according to any one of claims 10 to 17, wherein said
25 levomenthol is found at the concentration between 100 to 180 mg/l.