NEW UTILIZATION OF ALPHA-HIDROXY-PROPIONIC ACID IN MEDICINE

The present invention relates to a composition comprising alpha-hydroxy-propionic acid linked to any pharmaceutically acceptable vehicle, such as pure serum, 1,2,3-propanetriol, 1,2-propanediol resp. a mixture thereof or optionally a pharmaceutically acceptable catalyzer. Alpha-hydroxy-propionic acid is used in medicine in many dilutions for the treatment of sinusitis and other upper respiratory diseases. The present invention is characterized by a formulation adapted to nasal delivery for the treatment of upper respiratory disorders.
### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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"NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE"

The present invention is relative to a compound made of alpha-hidroxi-propionic (or 2-hidroxi-propionic), (compound I), combined with 1,2,3-propanotriol pure (glicerin), or to the 1,2-propanodiol pure or serum, or to a balanced mixture of them or any other acceptable pharmaceutic vehicle, (compound II) to the attaining procedures of such a compound or to its utilization in Medicine.

The invention has got a compound consisted of the alpha-hidroxi-propionic acid (compound I), or to an acceptable pharmaceutic salt of the latter, or of an acceptable pharmaceutic solvato of the latter, or of an acceptable pharmaceutic catalyser of the latter, characterized by the following dilution of:

0,2 to 0,9ml, or 1,1 to 2,0ml, or 2,1 to 3,0ml, or 3,1 to 4,0 ml, or 4,1 to 5,0ml, or 5,1 to 6,0ml, or 6,1 to 10ml of compound I in 100ml of compound II; and 0,3 to 0,8 ml, or 0,4 to 0,7 ml, or 0,2 to 0,5ml, or 0,5 to 0,9 ml, or 1,1 to 1,5ml, or 1,5 to 2,0ml, or 2,1 to 3,0ml, or 3,1 to 4,0ml, or 4,1 to 5,0 ml or 5,1 to 10,0 ml of the active principle of compound I in 100ml of compound II.

Compound I, in one or more of the above-mentioned items combined with compound II is characterized by being suit to the intake in drops, via the nasal airways, or as a spraying solution, a spray, a microfine powder for insufflation or an acceptable pharmaceutic salt or an acceptable pharmaceutic solvate for the medicine addressed to the treatment of the highairways disturbances.

There aren’t in the medical and pharmaceutical literatures any statements about the active principle of compound I. On the other hand, there isn’t an efficient medicine for the sinusitis treatment. What has been recorded in medical literature so far is the antibiotics massification which, besides its high cost, represents one of the biggest threats to the world public health, due to the development of resistant “cepas” (germs).

It’s to be pointed out that the antibiotics massification leads only to the
germs fight inside the organism or in its "doorway" when such disturbances are in acute crisis. During those crisis, the germs either in the nasal cavities or in the cheek bones located in external areas of the organism, in close contact with the external environment, aren't reached.

For a biologically active substance to carry out its duty, it's necessary to be positioned at the action location. The active principles are taken into the body through medicines. Therefore, it's necessary for them to be released in the location where the infectious agents are.

In fact, the antibiotic is a medicine for internal use and that's why it isn't efficient in the sinusitis treatment, taking into consideration that its release doesn't occur at the infection spot. As known, the sinusitis is an inflammation of the layer of the tissue that internally covers the cheek bones through little holes which communicate with the nasal cavity directly linked to the external environment.

As the application of compound I linked to compound II occurs at the nostrils, such a compound will work directly on the germs located in the nasal cavities and cheeks.

The first application effect in the nasal cavities and cheek bones of compound I linked to compound II is the "lisar" (dehydrating) of the germs that can be found there through its bactericide and bacteriostatic properties that are in contact.

After that, the hydrating and moistening effects of compound I linked to compound II, cause the increase in the nasal mucosa elasticity and its clearance. The action motion of the alpha-hidroxi-propionic acid keeps a more homogeneous cornea layer, decreasing the superficial cellular cohesion. Those alpha-hidroxi-propionic acids promote a subtle exfoliation, leaving the nasal mucosa smoother and more homogeneous.

As mediate effects, there are also the modifications of the medium pH, facilitating the "Lactobacillus acidophyllus" and the "Bifidobacteria" growth. The Bifidobacteria are known for displaying inhibiting effects upon many other

It's known, as well, that the bifidobacteria in the large intestine synthesize vitamins that are absorbed by the organism.

Bifidobacteria are still known for producing thiamine, riboflavin and vitamins B6 and K. It's still proved that the bifidobacteria are able to synthetize the complex B vitamins (Mutai, 1978).

In the cheek bones, the compound I linked to compound II changes the medium pH, promoting the mucosa hydrating which will speed up the bifidobacteria growth. The bifidobacteria, by competition, leaves out the pathogenic bacteria found there, which are responsible for the cheek bones infections. Then, the environmental adaptation to the new pH makes the cheek bones prone to the bifidobacteria development, as it occurs in the intestines (Rassic - 1989).

Well, similarly to the gastrointestinal tract, the respiratory system is open to the external environment in order to facilitate the organism breathing. In fact, the bifidobacteria and "Lactobacillus acidophilus" growth in the cheek bones, is possible due to the optimum pH, determined by the active principles of compound I linked to compound II.

Researches believe that the bifidobacteria, by competition, leave out the large intestines putrefying bacteria which are responsible for the free radicals release. The free radicals, being absorbed, will do the organism a lot of harm, such as early aging. (Metchnikoff, 1938 and Linnus Pauling, 1965)

Therefore, the "Lactobacillus acidophilus" and Bifidobacteria presences are beneficial to the cheek bones as well as to the intestines. One of the Bifidobacteria effects as an effective pathogenic germ inhibitor is associated with the production of lactats and acetats in small portions in the mechanism of
reaction in the chemical products resultant from the carbohydrates catabolism. Those elements and the pH inhibit the pathogenic bacteria growth. (Hughes, D.B., Hoover, D.G., BIFIDOBACTERIA, THEIR POTENTIAL FOR USE IN AMERICAN PRODUCTS).

The medicine utilization, represented by compound I linked to compound II is considered only by the otorhinolaryngologist clinics as a salutary alternative to the rhinitis and sinusitis treatment.

Carriers of such diseases feel considerable relief from the very first time they take the referred medicine.

The medicine, represented by compound I linked to compound II, has shown advantages upon any other medicine, for it isn’t reabsorbed for being a product of cellular rejects.

At present, the sinusitis is treated with last generation antibiotics, not always with the desired results for not reaching the infection focus, which is inaccessible, and its massification leads to one of the biggest threats to the world public health due to the resistant “cepas” (germs) appearance _ what would justify this request at once.

The alpha-hidroxi-propionic acid utilization (compound I), linked to the 1,2,3-propanotriol or to the 1,2-propanodiol (compound II) in the sinusitis treatment, besides being a profitable alternative in the treatment of those diseases, will bring huge social and economic benefits to the country.
REQUESTS

1. "NEW UTILIZATION OF THE ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE": characterized by a pharmaceutic compound, consisting of the alpha-hidroxi-propionic acid (compound I), or an acceptable pharmaceutic solution of the latter, linked to 1,2,3-propanotriol, or to 1,2-propanodiol, or to serum or any other acceptable pharmaceutic vehicle, (compound II), having in the composition the dilution of: 0.2 to 0.5ml, or 1.1 to 1.9ml, or 2.0 to 3.0ml, or 3.1 to 4.0ml, or 4.1 to 5.0ml, or 5.1 to 6.0ml, or 6.1 to 10ml of compound I in 100ml of compound II; and still 0.3 to 0.8ml, or 0.4 to 0.7ml or 0.5 to 0.9ml, or or 1.1 to 1.9 ml, or 2.0 to 2.5ml, or 2.5 to 3.0ml, or 3.1 to 4.0ml, or 4.1 to 5.0ml or 5.1 to 10,0ml of the active principle of compound I in 100ml of compound II.

2. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC IN MEDICINE", according to request I, characterized by its utilization in the sinusitis and other highairways diseases.

3. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC IN MEDICINE", according to request I, characterized by its utilization in the human and veterinarian highairway treatment.

4. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE", according to request I, characterized by its utilization as nasal releaser.

5. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE", according to request I, characterized by its dilution in 100ml of 1,2,3-propanotriol (compound II).

6. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE", according to request I, characterized by its utilization as a medication in the sinusitis and rhinitis treatment and as a clearing agent of the nasal cavities.

7. "NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC
ACID IN MEDICINE”, according to request I, characterized by its dilution in 100 ml of serum or any other acceptable pharmaceutic vehicle of the latter.

8. “NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE”, according to request I, characterized by its dilution in 100 ml of serum or any other acceptable pharmaceutic vehicle of the latter.

9. “NEW UTILIZATION OF ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE”, according to request I, characterized by the dilution in 10 ml of 1,2-propanediol (compound II).

10. “NEW UTILIZATION OF THE ALPHA-HIDROXI-PROPIONIC ACID IN MEDICINE”, according to request I, characterized by being adapted for intake in drops, via nasal airways, or in the form of a solution for spraying, or a spray, a microfine powder for insufflation or an acceptable pharmaceutic salt of the latter, or an acceptable pharmaceutic solvate of the latter, so that a medicine can be prepared to the treatment of human and veterinarian highairways disturbances.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC*: A61K 31/191, 31/22, 9/08, 9/72

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC*: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, PAJ, EPODOC, medline, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
& document member of the same patent family

Date of the actual completion of the international search

05 April 2000 (05.04.00)

Date of mailing of the international search report

17 April 2000 (17.04.00)

Name and mailing address of the ISA/AT
Austrian Patent Office
Kohlmarkt 8-10; A-1014 Vienna
Facsimile No. 1/53424/200

Authorized officer
Krenn

Telephone No. 1/53424/435

Form PCT/ISA/210 (second sheet) (July 1998)
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: (please see remark)
   because they relate to subject matter not required to be searched by this Authority, namely:
   Remark:
   Although the formulation “New utilization of ... in medicine ...” is quite imprecise and might involve therapeutic methods of treatment of the human/animal body, the search has been carried out for all claims and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying and additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1998)
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