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(71) Applicant *(for all designated States except US)*: **NATURE'S PLUS FARMACÊUTICA LTDA.** [BR/BR]; Rodovia SP 110, Km 108, 13186-481 Hortolândia (BR).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **VANDONI, Guido** [IT/IT]; Via Principale, 30, I-20050 Correzzana (IT). **OLIANI, Carlo** [BR/BR]; Rodovia SP 101, Km 08, 13186-481 Hortolândia (BR). **COELHO, Adriano** [BR/BR]; Rodovia SP 101, Km 08, 13186-481 Hortolândia (BR). **ZANIBONI, Heny** [BR/BR]; Rodovia SP 101, Km 08, 13186-481 Hortolândia (BR).

(74) Agent: **LLC INFO CONNECTION LTDA.**; 5555 Dom Hélder Câmara Av., Rm 312, Pilares, 20771-001 Rio de Janeiro (BR).

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(54) Title: PHARMACEUTICAL COMPOSITION BASED ON KETOROLAC OR ONE OF ITS SALTS PHARMACEUTICALLY ACCEPTABLE AND USE OF KETOROLAC OR ITS SALTS IN PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention refers to pharmaceutical compositions based on ketorolac or one of its salts pharmaceutically acceptable, as well as the use of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, for preparation of a pharmaceutical composition (tablets) for sublingual administration, with the purpose of accelerating the pharmacological response to ketorolac, without making use of the injectable via. On the other hand, a pharmaceutical composition is described encompassing, as one of its active principles, ketorolac or one of its salts acceptable from pharmaceutical viewpoint, representing from 10 to 15% by weight, in relation to the total weight of the compound and as the essential excipient, a ternary mixture of lactose/sorbitol/cellulose, eventually in a mixture with other excipients acceptable from pharmaceutical viewpoint.

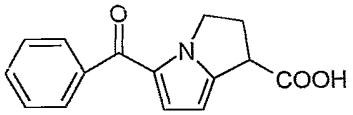
"PHARMACEUTICAL COMPOSITION BASED ON KETOROLAC OR ONE OF ITS SALTS PHARMACEUTICALLY ACCEPTABLE AND USE OF KETOROLAC OR ITS SALTS IN PHARMACEUTICAL COMPOSITIONS".

Field of the Invention

The present invention refers to the use of ketorolac or one of its salts, acceptable from pharmaceutical point of view, for preparation of a pharmaceutical composition in tablets, for sublingual administration, to accelerate the pharmaceutical response, especially the analgesic response by the use of ketorolac.

State of the Art

Ketorolac is a medicament inhibitor of prostaglandin synthesis, which formula is



notably known by its anti-inflammatory, analgesic and antipyretic action as described in Patent US 4,089,969, in which tromethamol salt is used in its racemic form.

Pharmaceutical formulations with analgesic and antipyretic action, containing R form, were also described in the state of the art, as can be noted in the patent document EP 674511. It should also be emphasized that ketorolac may be used for the therapy in periodontal affection treatments, as described in patent document WO 91/13609, and for the treatment of carcinomas of the scaly cells in the oral cavity or of the oropharynx, as taught in the patent document WO 96/28144.

In the several indications mentioned in the literature, ketorolac was proposed using several

administration routes. For example, Patent US 4,089,969 suggests the oral, parenteral or topic administration, in several pharmaceutical forms, particularly in tablets, suppository, pills, capsules, powder, solutions, suspensions, emulsions, creams, lotions and unguents.

However, patent document WO 91/13609 suggests the application of ketorolac through dentifrices, solutions for mouthwash, spray for oral cavity or dental solutions. The latter type of ketorolac application is also suggested in patent document WO 96/28144.

The Patent US 6,090,368 describes the nasal spray, whereas patent document WO 99/09954 describes a compound for skin topic administration and patent document EP 668759 describes ketorolac administration by transdermic via.

Currently, ketorolac, in the form of tromethanol salt is used by oral via in tablets of 10 mg or dropwise, in a solution of 2%, by injectable via, being provided in flasks of 10 or 30 mg, and by rectal via in suppositories of 30 mg.

Consequently, in order to obtain a rapid anti-inflammatory, antipyretic and analgesic action of ketorolac, the single current possibility is to make use of the injectable administration via, which knowingly causes slight illness and discomfort to the patient. Particularly due to its use as analgesic, a greater speed of ketorolac action assumes a significant importance.

Summary of the Invention

It was recently proved that with ketorolac

administration or one of its salts acceptable from pharmaceutical viewpoint, more particularly its tromethamol salt by sublingual via, the absorption of the active principle is more rapidly obtained than in comparison with the oral administration, thus resulting in a more rapid therapeutic action with plasmatic levels of the active principle equal or very close to those obtained after the traditional oral administration, which results in a therapeutic activity very close, if not equal to the previous one, or even better.

On the other hand, it was proved that a pharmaceutical composition composed by the *essential carrier* containing 10-15% in weight of ketorolac or one of its salts acceptable from pharmaceutical point of view, preferably tromethamol ketorolac, and with at least 60% of the total weight of the compound represented by *essential excipients*, composed by ternary mixture of lactose/sorbitol/cellulose in the respective weight percentages (in relation to the total weight of the compound) of 30-50%/3-9%/9-17%, is rapidly absorbed by sublingual via, allowing to achieve the hematic levels of ketorolac rapidly, with sufficient value to assure the therapeutic activity desired in the above mentioned indications, particularly in relation to the analgesic property.

The term "*essential carrier*" refers to the pharmaceutical composition containing a mixture of the active principle of ketorolac compound or one of its salts acceptable from pharmaceutical viewpoint, particularly its

tromethamol salt, an excipient necessary to compose the formulation, which is presented in the form of sublingual tablets for oral administration, specially including the essential excipients. The term "*essential excipients*" refers to the mixture of the excipients or the ternary mixture lactose/sorbitol/cellulose in specific proportions (lactose (30-50% in weight)/sorbitol (3-9% in weight)/ cellulose (9-17% in weight). The term "*ternary mixture*" refers to the three excipients, lactose/sorbitol/ cellulose. Hereinafter, the terms essential carrier, essential excipients and ternary mixture will appear in the present document meaning the foregoing explanation.

The term "ketorolac" represents the International Common Denomination" (DCI) of the racemic form of 5-benzyl-2,3-dihydro-1H-pyrrolizin-1-carboxylic acid.

The term "tromethamol" represents the DCI of 2-amino-2-(hydroxymethyl)-1,3-propanediol, also indicated as "tromethamine" in USP dictionary of pharmaceutical products.

The expression "tromethamol ketorolac", specifically designates the tromethamol ketorolac salt.

Detailed Description of the Invention

According to one of its aspects, the present invention refers to the use of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, for the preparation of a pharmaceutical composition for sublingual administration destined to accelerate the pharmacological response to ketorolac without making use of the injectable via. It is understood by the term "sublingual", the

application of the active principle through the administration of the pharmaceutical composition in the said sublingual form, i.e., under the tongue or gingiva, i.e., placing the tablet between the cheek and the gingiva.

It is understood that the expression "pharmacological response to ketorolac" refers to the response due to the systemic action of ketorolac itself or one of its salts acceptable from pharmaceutical viewpoint, preferably the tromethamol salt, in the treatment of the aforementioned diseases.

One of the advantageous uses of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, consists of the preparation of a pharmaceutical composition for sublingual administration with the purpose of accelerating the analgesic response of ketorolac without making use of the injectable via. Even more advantageous, the invention refers to the use of tromethamol ketorolac for preparation of the pharmaceutical compounds for sublingual administration destined to accelerate the analgesic response of ketorolac without making use of the injectable via.

According to one of its other aspects, the present invention provides a pharmaceutical composition for sublingual use, due to the quality of one of its principle actives, reaching from 10 to 15% in weight of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, mixed with a pharmaceutical excipient formed by, at least, 60% in relation to the total weight of the excipients of a diluent composed of a polyalcohol derivative from reduction

of a monosaccharide and a carbohydrate, at least.

In the present context, unless otherwise indicated, the specific indication of the percentages is given in weight and refers to the total weight of the composition.

The referred pharmaceutical composition may promote the acceleration of ketorolac pharmacological response. It is composed of tablets for sublingual administration containing from 2 to 15 mg of ketorolac or one of its salts acceptable from pharmaceutical viewpoint. The same is particularly destined to the rapid induction of the analgesia in patients requiring this rapid induction.

The recommended dosage unit of the referred to agonists is composed of 2.5; 5 or 10 mg of ketorolac, preferably tromethamol ketorolac mixed with excipients, of which, at least, 60% is composed of a polyalcohol derivative of a monosaccharide and of, at least, a carbohydrate, and eventually, other excipients as lubricants, aggregate, sweetening, taste correctors (flavors) and casually, disaggregating agents used in the manufacture of pills and tablets for sublingual use.

Are considered as advantageous excipients or essential excipients, those excipients used in quantity of at least 60% in weight in relation to the total weight of the composition, the carbohydrates as cellulose powder, microcrystalline cellulose or sodium carboxy-methylcellulose, lactose, corn or potato starch, natural or modified, or mixtures thereof and polyalcohol derivatives from reduction of monosaccharides as D-mannitol, L-glucitol

and especially, D-glucitol or sorbitol, which may also act as sweetening agent.

In relation to the other excipients, the lubricants as polyethyleneglycol, especially polyethylene-glycol 6000 are used in quantities corresponding to 0-5% by weight, the aggregative as microcrystalline silica are advantageously being used with weight ranging between 0,5 and 5%, the disaggregating agent as polyvinyl pyrrolidone generally represents from 5 to 10% by weight. In practice, carbohydrates and derivatives thereof, essentially compose the excipients of the composition of the present invention.

Due to the sublingual use of the pharmaceutical preparation of the present invention, the sweetening and/or the flavors constitute an essential presence and will be chosen by experts of the area, in relation to the organoleptic characteristics of any of the active principles. The natural sweetening are advantageously being used, including mannitol and sorbitol, which in this case are part of the diluents, the latter being used in quantities corresponding to 3-9%, whereas the synthetic sweetening as sodium saccharine or aspartame are used in quantities of 0.1-5%.

The flavors incorporated to the composition may also be chosen among the flavors of synthetic or natural oils, encompassing plant, leaf, flower, fruit extracts and combinations thereof, as cinnamon, *mentha piperita*, anise, cedar leaves, bitter almond, citrus fruits, especially orange and lemon, chamomile and grapefruit. The tropical flavors as vanilla or eucalyptus flavor, and fruit

essences, especially apple, pear, peach, raspberry, cherry and grape may be advantageously used.

Generally, the flavors are present in quantities ranging from 0.05% to 4% of the total weight of the compound. The preferred flavors are the tropical flavors and those that give mint or fruit taste, particularly of grape, cherry or citric fruits, especially orange, lemon or mixtures thereof.

According to another aspects thereof, the present invention provides a pharmaceutical composition that comprises 10-15% by weight of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, preferably from 60 to 75% of the total weight of the compound of an essential excipient, composed of a ternary mixture of lactose/sorbitol/cellulose, in the respective weight percentages (in relation to the total weight of the compound) of 30-50% /3-9% /9-17%, preferably of 40-50% /5-8%/12-14%. Preferably, in the referred to essential excipient, the relation lactose/cellulose is of approximately 2.5/1 close to 3.5/1, and sorbitol represents 6-8% of the total weight of the compound. The referred to pharmaceutical composition is found in dosage units of, for example, tablets containing from 2 to 15 mg, preferably 2.5; 5 or 10 mg of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, preferably tromethamol ketorolac. This type of tablets is especially appropriate for sublingual administration.

According to a preferential aspect of the invention, the referred to essential excipient is composed

of a mixture of lactose (45-48% by weight)/sorbitol (5-8% by weight)/cellulose (12-15% by weight), which weight relation lactose/sorbitol/cellulose is of 3±0,5/ 0,6±0,2/1, eventually in a mixture with other excipients acceptable from pharmaceutical viewpoint.

The essential excipients, composed of the mixture lactose/sorbitol/cellulose in the referred to weight percentages, in relation to the total weight of the compound is preferably a mixture with a proportion of approximately 3/0.4-0.7/1, containing ternary mixture forming the essential excipients in the weight percentages, each one always referring to the total weight of the compound, lactose (30-50%)/sorbitol (3-9%)/cellulose (9-17%).

The referred to composition is particularly indicated for sublingual administration.

In addition to the essential excipients, lactose/sorbitol/cellulose, the composition of the invention may contain other excipients, especially disaggregating agents, as polyvinyl pyrrolidone, corn or potato starch, eventually modified, lubricants as magnesium stearate, aggregative agents, as methylcellulose, sodium carboxymethylcellulose, polyethyleneglycol, silica microcrystalline, colloidal silicon dioxide, magnesium and aluminum silicate, dyers as titanium dioxide, sweetening and flavors as previously mentioned.

The composition of the present invention may contain excipients that give it effervescence during the permanence under the tongue. The advantageous excipients of

this type of composition are the mixtures of acids and carbonates, adequately prepared in accordance with the usual techniques, especially citric or tartaric acid and sodium, potassium or magnesium carbonate or bicarbonate.

The tablets for sublingual administration of the present invention may be manufactured in accordance with the classic methods used in pharmaceutical technique, for example, by direct compression, by humid granulation or using technology of active principle incorporation in micro-granules, microsphere or micro-emulsions, allowing better absorption of the referred to active principle.

The composition of the present invention will be prepared according to methods of pharmaceutical technique. In practice, the calculated quantity of tromethamol ketorolac, of sorbitol, preferably micro-granulated and one aggregative, for example, sodium carboxymethyl-cellulose, will pass through a sieve and mixed for 10-15 minutes. To this mixture will be added the calculated quantity of lactose, cellulose, preferably micronized, of a disaggregate as polyvinyl pyrrolidone or crospovidone, for example, Polyplasdone XL, of a ligand as colloidal silicon, for example, Syloid 244, of a flavor and a sweetening, making all these excipients pass through a sieve of 30 mesh and mixing everything for further 10-15 minutes. To the mixture thus obtained will be added the calculated quantity of a lubricant, for example, magnesium stearate or polyethyleneglycol, mixing for some minutes and making the compression of the mixture with appropriate punctures.

The composition of the present invention, after

administration of a dose of 10 mg, enables the hematic rates of ketorolac to be rapidly reached, thus ensuring rapid analgesic or anti-inflammatory action.

The bioavailability after the sublingual administration of a single dose of 10 mg of tromethamol ketorolac was compared with the same single dose of the active principle in conventional oral tablets, in a study with twelve healthy male volunteers recruited after the respective information on the nature and characteristics of the active principles and also on the scope of the study. The referred to study, composed of four treatment periods, was carried out according to a crossed and randomized scheme.

All individuals received the pre-established dose of the active principle in the form of conventional oral tablets, in the form of sublingual tablets, by endovenous and intramuscular via, within a washout period of at least seven days after the first treatment and each subsequent treatment, according to a pre-established list of randomization. The sublingual tablets were placed under the tongue in correspondence with the venous plexus, until its complete dissolution, whereas the conventional oral tablets were swallowed unbroken with 150 ml of mineral water. Five ml of venous blood were collected in the periods 0-5-10-20-40 minutes, 1-2-4-8 and 24 hours after the treatment. Table I shows the average plasmatic rates measured after the single doses mentioned.

Table I

	0	5 minutes	10 minutes	20 minutes	40 minutes	1 hour	2 hours	4 hours	8 hours	24 hours
E.V.	0	315,83 ± 136,09	2858,89 ± 680,35	1096,58 ± 376,46	794,31 ± 274,46	637,20 ± 243,46	504,58 ± 228,98	332,41 ±177,30	156,80 ± 83,02	16,21 ± 18,04
I.M.	0	5,70 ± 10,39	119,09 ± 56,83	245,20 ± 115,17	543,08 ± 316,31	720,04 ± 201,80	448,85 ± 117,88	323,04 ± 103,29	193,88 ± 63,74	25,63 ± 19,82
Conventional Tablet	0	0	43,73 ± 42,88	227,15 ± 73,17	660,69 ± 303,43	730,60 ± 235,35	480,28 ± 232,68	317,03 ± 190,96	161,04 ± 87,83	26,29 ± 22,94
Sublingual Tablet	0	43,28 ± 31,81	205,26 ± 95,16	736,30 ± 275,13	776,28 ± 287,80	626,88 ± 260,98	429,04 ± 212,33	305,71 ± 182,59	158,35 ± 97,70	25,41 ± 25,46

In above table, exactly in the first minutes after the sublingual administration, can be observed a tendency for obtaining hematic rates higher in relation to those obtained after administration of the same dose by oral or intramuscular via, whereas the other plasmatic rates can be easily overcome.

Table II shows the data referring to the several pharmacokinetic parameters (average ± standard deviation) referring to sublingual, conventional oral, endovenous and intramuscular administration of tromethanol ketorolac. Especially the AUC_{0-t} informed in the Table, i.e., the area under the time curve 0 up to time T (in this case, at hour 24), its logarithm AUC_{0-inf} (in ng/ml/h) i.e., the area under

the curve according to the formula

$$AUC_{0-inf} = AUC_{0-t} + C_{t/b}$$

in which C_t is the plasmatic concentration (in ng/ml) estimated at time T (in this case, at hour 24) and b is the slope of the curve of the washout phase, being its logarithm, the C_{max} (in ng/ml), i.e., the peak of maximum concentration, its logarithm and the T_{max}, i.e., the time (in hours) in which the maximum plasmatic concentration peak is compared.

Table II

PHARMACOKINETIC PARAMETERS	Sublingual Tablets	Conventional Tablets	E.V.	I.M.
AUC $_{0-t}$ (ng/ml/h)	237972,81 ± 141094,58	233989,13 ± 118781,73	260432,85 ± 141307,54	260002,03 ± 96077,99
AUC $_{0-inf}$ (ng/ml/h)	258205,10 ± 143740,06	263791,13 ± 124504,49	281323,89 ± 140122,03	278349,95 ± 92737,20
Log AUC $_{0-t}$	5,30 ± 0,28	5,31 ± 0,24	5,36 ± 0,22	5,38 ± 0,22
Log AUC $_{0-inf}$	5,34 ± 0,27	5,37 ± 0,24	5,40 ± 0,21	5,41 ± 0,19
C_{max} (ng/ml)	991,47 ± 219,40	871,28 ± 236,90	2858,89 ± 680,35	835,31 ± 196,13
Log C_{max}	2,99 ± 0,10	2,92 ± 0,13	3,45 ± 0,10	2,91 ± 0,11
T_{max} (min)	33,33 ±13,03	53,33 ± 9,85	10 -	51,67 ± 10,30

From the statistic analyses made from all pharmacokinetic parameters, using the analysis of variance (ANOVA) and the test of Bonferroni, and also only on the T_{max} parameter, the tests for the data in pairs of Wilcoxon, did not result in significant differences in the treatments

with reference to $\log AUC_{0-inf}$, either in ANOVA test or in Bonferroni test, while a significant difference can be observed between the endovenous treatment and the other ways of administration with reference to $\log C_{Max}$. With reference to T_{max} parameter, it was observed that either in ANOVA test or in Bonferroni and Wilcoxon tests, there is a significant difference between the treatment by sublingual via and those by conventional oral or intramuscular via. It was especially evidenced that the sublingual treatment presents a T_{max} significantly shorter in relation to the conventional oral or intramuscular treatment, considered equal between it.

The following examples explain the invention, however, without limiting the same.

EXAMPLE 1

A mixture of 1.000 kg of tromethamol ketorolac, 0.500 kg of micro-granulated sorbitol and 0.200 kg of sodium carboxymethylcellulose is passed through a sieve of 30 mesh, and after that, mixed for 10 minutes. Add to this mixture, 3.375 kg of lactose, 1.125 kg of micronized cellulose, 0.150 kg of sodium saccharine, 0.6 kg of Polyplasdone XL, 0.100 kg of Syloid 244 and 0.250 kg of lemon flavor, previously passed through a sieve of 30 mesh. Slurry the mixture for 10 minutes. Add 0.200 kg of magnesium stearate previously passed through a sieve of 30 mesh. Slurry the end-mixture for 3 minutes. Promote the compression in an alternative or rotating compression machine, provided with punctures with 6 mm diameter. Thus, 100,000 tablets will be obtained with a weight of 75 mg

each, with a formulation showing the following composition:

Tromethamol Ketorolac	10.00 mg
Lactose	33.75 mg
Sorbitol	5.00 mg
Micronized Cellulose	11.25 mg
Sodium Carboxymethylcellulose	2.00 mg
Sodium Saccharine	1.50 mg
Polyplasdone XL	6.00 mg
Syloid 244	1.00 mg
Lemon flavor	2.50 mg
Magnesium stearate	2.00 mg

The tromethamol ketorolac tablets for sublingual administration thus obtained, contain 13.33% of active principle and 66.67% of essential excipients, among which lactose represents 45% of the total compound, sorbitol representing 6.67% of the total compound and cellulose representing 15% of the total compound, being the proportion of lactose/sorbitol/cellulose of 3/0.44/1.

EXAMPLE 2

Carrying out the same operation described in Example 1 above, with 1.000 kg of tromethamol ketorolac, 4.500 kg of Cellactose, composed of a mixture containing 75% of lactose and 15% of cellulose, 0.500 kg of micro-granulated sorbitol, 0.200 kg of sodium carboxymethyl-cellulose, 0.600 kg of polyvinyl pyrrolidone (Collidon C1 BASF), 0.250 kg of lemon flavor (15203-71/MD-Givaudan), 0.100 kg of microcrystalline silica (Syloid 244), 0.200 kg of magnesium stearate and 0.150 kg of sodium saccharine 100,000 tablets will be prepared with a weight of 75 mg

each, presenting the following composition:

Tromethamol Ketorolac	10.00 mg
Lactose	33.75 mg
Microcrystalline Cellulose	11.25 mg
Microgranulated Sorbitol	5.00 mg
Polyvinyl pyrrolidone	6.00 mg
Sodium Carboxymethylcellulose	2.00 mg
Lemon flavor	2.50 mg
Sodium Saccharine	1.50 mg
Magnesium stearate	2.00 mg
Microcrystalline Silica	1.00 mg

The tromethamol ketorolac tablets for sublingual administration thus obtained contain 13.33% of active principle and 66.67% of essential excipients, among which lactose represents 45% of the total compound, sorbitol representing 6.67% of the total compound and cellulose representing 15% of the total compound, being 3/0.44/1 the respective proportion of lactose/sorbitol/cellulose.

CLAIMS

1. **PHARMACEUTICAL COMPOSITION BASED ON KETOROLAC OR ONE OF ITS SALTS PHARMACEUTICALLY ACCEPTABLE,** characterized by the use of ketorolac or one to its salts acceptable from pharmaceutical viewpoint for preparation of pharmaceutical compositions for sublingual administration, destined to accelerate the pharmacological response to ketorolac, without making use of injectable via.

2. **PHARMACEUTICAL COMPOSITION,** according to claim 1, characterized for its sublingual use, encompassing as one of its active principles, from 10 to 15% by weight of ketorolac or one of its salts acceptable from the pharmaceutical viewpoint, constituting, at lest, 60% in relation to the total weight of the excipients, of a diluent composed by a polyalcohol derivative from reduction of a monosaccharide and, at least, a carbohydrate.

3. **PHARMACEUTICAL COMPOSITION,** according to claim 1 or 2, characterized for consisting from 10 to 15% by weight of ketocolac or one of its salts acceptable from pharmaceutical viewpoint and, at least, 60% of essential excipients composed of a mixture of lactose/sorbitol/cellulose with the respective weight percentages of 30-50%/3-9%/9/17%.

4. **PHARMACEUTICAL COMPOSITION,** according to claim 3 above, characterized by the fact that the referred to essential excipient represents 60-75% of its total weight.

5. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 or 4 above, characterized by the fact that the referred to essential excipient is composed of a mixture of lactose (45-48%)/sorbitol (6-8%)/cellulose (12-15%).

6. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 to 5, characterized by the fact that the mixture lactose/cellulose of the referred to essential excipient, is shown in the proportion lactose/cellulose of approximately 2.5/1 up to approximately 3.5/1, and sorbitol represents 6-8% of the total weight of the compound.

7. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 to 6, characterized by the fact that in the referred to essential excipient, the proportion lactose/sorbitol/cellulose is of approximately 3±0.5/0.6±0.2/1.

8. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 to 7, characterized by the fact that in the referred to essential excipient, the proportion lactose/sorbitol/cellulose is of approximately 3/0.4-0.7/1.

9. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 to 8, characterized by the fact that the referred to essential excipient is a mixture of excipients acceptable from pharmaceutical viewpoint.

10. **PHARMACEUTICAL COMPOSITION**, according to one of the claims 3 to 9, characterized by the fact that the same contains from 2 to 15 mg of ketorolac or one of its salts acceptable from pharmaceutical viewpoint.

11. **PHARMACEUTICAL COMPOSITION** according to claim 10, characterized by the fact that the referred to salt acceptable from pharmaceutical viewpoint is tromethamol salt.

12. **PHARMACEUTICAL COMPOSITION**, according to one of the claim 10 or 11, characterized by the fact that the said composition contains 2.5, 5 or 10 mg of tromethamol ketorolac.

13. **PHARMACEUTICAL COMPOSITION**, in the sublingual form, according to claim 1, characterized for being formulated to accelarate the pharmacological response to ketorolac, in the form of tablets for sublingual administration, containing from 2 to 15 mg of ketorolac or one of its salts acceptable from pharmaceutical viewpoint, mixed with a pharmaceutical excipient composed of, at least, 60% of diluents composed of a polyalcohol derivative from reduction of a monosaccharide and, at least, one carbohydrate, in relation to the total weight of the excipients.

14. **PHARMACEUTICAL COMPOSITION**, according to claim 13, characterized by the fact that the said composition consists of at least 60% of an essential excipient composed of a ternary mixture of lactose/sorbitol/cellulose in the respective percentages in weight of 30-50%/3-9%/9-17%.

15. **PHARMACEUTICAL COMPOSITION**, according to one of claims 13 or 14, characterized by the fact that in the referred to essential excipient, the proportion lactose/sorbitol/cellulose is of approximately 3±0.5/0.6±0.2/1.

16. **PHARMACEUTICAL COMPOSITION**, according to one of claims 15 to 17, characterized by the fact that the referred to pharmacological response to ketorolac is the rapid induction of analgesia.

17. **Use of ketorolac** or one of its salts acceptable from pharmaceutical viewpoint, characterized by the fact of being for the preparation of pharmaceutical compositions for sublingual administration, destined to accelerate the pharmacological response to ketorolac without making use of the injectable via.

18. **Use**, according to claim 17, characterized by the fact that this pharmacological response is the analgesic response to ketorolac.