

PATENT COOPERATION TREATY

TRANSLATION

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:

Date of mailing **31.03.2022**
(day/month/year)

Applicant's or agent's file reference

78015-PCT

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/CL2021/050060

International filing date (day/month/year)

02.07.2021

Priority date (day/month/year)

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

A61K8/22, 31/05, 31/055, 31/125, 31/327, 33/40, A61Q 11/00, A61P 31/00, 31/02, 31/04(2022.01

Applicant

INGALFARMA SPA

1. This opinion contains indications relating to the following items:

- | | | |
|-------------------------------------|--------------|--|
| ☒ | Box No. I | Basis of the opinion |
| ☐ | Box No. II | Priority |
| ☒ | Box No. III | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability |
| ☐ | Box No. IV | Lack of unity of invention |
| ☒ | Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| ☐ | Box No. VI | Certain documents cited |
| ☐ | Box No. VII | Certain defects in the international application |
| ☒ | Box No. VIII | Certain observations on the international application |

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA/CL

Date of completion of this opinion

Authorized officer

Facsimile No.

Telephone No.

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Box No. I **Basis of this opinion**

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed
 - ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(b))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. III **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. **34-39**

because:

☒ the said international application, or the said claims Nos. **34-39** relate to the following subject matter which does not require an international search (*specify*):

Claims 34-39 relate to subject matter considered by this Authority to be covered by PCT Rule 39.1(iv), concerning methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods. In conclusion, no expert opinion will be established for the novelty, inventive step and industrial applicability of said claims (Article 17(2)(a)(b)).

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):

☒ no international search report has been established for said claims Nos. **34-39**

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

☐ furnish a sequence listing in the form of an Annex C/ST.25 text file, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ furnish a sequence listing on paper or in the form of an image file complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in the form and manner acceptable to it; or the sequence listing furnished did not comply with the standard provided for in Annex C of the Administrative Instructions.

☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rule 13ter.1(a) or (b).

☐ See Supplemental Box for further details.

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Box No. V	Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement		
1. Statement			
Novelty (N)	Claims	1-33	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-33	NO
Industrial applicability (IA)	Claims	1-33	YES
	Claims	NONE	NO
2. Citations and explanations:			
Reference is made to the following documents: D1 KAMINSKA, M. et al. Effects of statins on multispecies oral biofilm identify simvastatin as a drug candidate targeting Porphyromonas gingivalis, 2018. D2 DAS, S. et al. Determination of the Antibacterial Activity of Atorvastatin against Periodontal Pathogens, Aggregatibacter actinomycetemcomitans and Porphyromonas gingivalis: An in vitro Study, 30 April 2020. D3 CARDENAS, A et al. Sistemas de administración de estatinas en el tratamiento de la periodontitis: una revisión de literatura, 1 November 2018. D4 W02014121411 A1 (GALVAN, T.), 14 August 2014. D5 US8865136 B2 (GALVAN, T.), 21 October 2014. Analysis of Novelty. The invention as defined in claims 1-33 is novel and therefore meets the provisions of PCT Article 33(2). Documents D1, D2 and D3 are considered the closest prior			

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art documents.

Document D1 discloses that several studies have attributed statins with immunomodulatory and bactericidal properties, in addition to their already known effect of reducing cholesterol levels. In that respect, the aim of this document is to investigate the antimicrobial activity of the statins atorvastatin, fluvastatin, lovastatin and simvastatin against periodontal homeostasis bacteria. In that sense, this study observes the statin effect on bacterial growth using multibacterial biofilms from five microbial species (*Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Actinomyces naeslundii*, *Tannerella forsythia*, and *Streptococcus gordonii*) associated with dysbiosis of the oral microbiota underlying establishment and perpetuation of periodontitis. As a result, this document shows that the tested statins efficiently inhibited the growth of the studied bacteria and significantly decreased the cumulative bacterial load in developing and established biofilms. Likewise, it can be demonstrated that simvastatin is most efficient, since decreased *P. gingivalis* counts more than 1,300-fold relative to the control, exhibiting a Minimum Bactericidal Concentration (MBC) of 0.001% (1 µg/ml) and an Minimum Inhibitory Concentration (MIC) of 0.01% (10 µg/ml) for *P. gingivalis*, while not affecting commensal microbiota, and which possesses many properties qualifying it as a potential adjunctive treatment for chronic periodontitis. Nevertheless, this document does not disclose an oral pharmaceutical composition comprising a statin and at least one antiseptic and/or antibacterial agent such as

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that which is disclosed in claim 1 of the application under analysis, nor does it disclose any of the pharmaceutical formulations comprising the pharmaceutical composition of the present invention, nor the use of the composition disclosed for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth that are present in the oral cavity such as gingivitis and periodontitis, nor a pharmaceutical kit for oral use comprising the composition of the present invention.

Therefore, claims 1-33 are novel in view of this document.

Document D2 mentions a study to determine the antimicrobial activity or effect of atorvastatin against the primary periodontal pathogens. This study evaluates the antimicrobial effect of atorvastatin against the bacteria *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, for which Minimum Inhibitory Concentrations (CIM) and Minimum Bactericidal Concentrations (CBM) are used. It was found that both bacteria are sensitive to pure atorvastatin. The data obtained in this document further suggest a potent antimicrobial activity of atorvastatin against *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. Therefore, it is observed that atorvastatin can be prescribed in patients suffering from periodontal disease. Likewise, this document establishes that, in the oral cavity, the bacteria *A. actinomycetemcomitans* and *P. gingivalis* are considered major pathogens for initiation and progression of the destruction of tooth supporting structures which can increase periodontal conditions

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(diseases of the hard tissue surrounding the tooth). It also indicates that the statins have a number of pleiotropic effects such as anti-inflammatory, immunomodulatory and antioxidant, which in turn have anti-bone resorptive property. Thus, this document mentions that atorvastatin exhibits good applicability in the periodontics field as local drug administration agent due to its anti-inflammatory properties, bone regenerative properties and as antimicrobial agent. However, this document does not disclose an oral pharmaceutical composition comprising a statin and at least one antiseptic and/or antibacterial agent such as that which is disclosed in claim 1 of the present application, nor does it disclose any of the pharmaceutical formulations comprising the pharmaceutical composition of the present invention, nor the use of the composition disclosed for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth that are present in the oral cavity such as gingivitis and periodontitis, nor a pharmaceutical kit for oral use comprising the composition of the present invention.

Therefore, claims 1-33 are novel in view of this document.

Document D3 mentions that periodontitis (inflammation of the periodontal tissues) can cause destruction of the tooth supporting tissues, causing bone and dental loss. Furthermore, it indicates that chronic periodontitis is caused by periodontal pathogenic bacteria such as *Porphyromonas gingivalis*, *Aggregatibacter actinomycetemcomitans*, *Tannerella forsythia* and *Treponema*

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denticola, which activate the innate and adaptive immune system. Likewise, this document indicates that the treatment of periodontal disease involves non-surgical strategies such as scaling and root planing and the administration of systemic and local antibiotics such as metronidazole, amoxicillin, tetracyclines, as well as the use of statins; drugs mainly used against hyperlipidaemia such as simvastatin. It also states that statins can be currently prescribed as a dual action drug, both in patients suffering from hyperlipidaemia and those suffering from periodontal disease. Moreover, it mentions that the most used molecules are simvastatin, atorvastatin and lovastatin. It also states that the use of statins in periodontal disease is due to their anti-inflammatory effect, in addition to stimulating bone formation, angiogenesis and their antimicrobial activity. Furthermore, this document establishes that different administration media have been used for the application of these drugs in the treatment of chronic periodontitis, which include gels, fibres, films, blisters and nanoparticles. The gel stands out as the preferred system to release and transport statins, which decreases adverse effect of the systemic administration due to its anti-inflammatory effects, as well as its antioxidant capacity, among others, and because of their higher efficiency for bone scarring. Similarly, it indicates that, in periodontology, statins have shown a decrease in clinical periodontal parameters after 6 months of treatment and that when they are applied topically, they can counteract inflammation and lead to the regeneration of soft and hard tissues in the treatment of periodontal disease, without the adverse effects of oral

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administration. It states that statins in gel form are the best option, especially simvastatin in a methylcellulose gel at 1.2% followed by atorvastatin. Statins are used in periodontal disease due to their anti-inflammatory effect, in addition to stimulating bone formation, angiogenesis and their antimicrobial activity. Therefore, topically applied statins can counteract inflammation and lead to the regeneration of soft and hard tissues in the treatment of periodontal disease, without causing the adverse effects of oral administration. Despite all this, this document does not disclose an oral pharmaceutical composition comprising a statin and at least one antiseptic and/or antibacterial agent such as that which is disclosed in claim 1 of the present application, nor does it disclose any of the pharmaceutical formulations comprising the pharmaceutical composition of the present invention, nor the use of the composition disclosed for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth present in the oral cavity such as gingivitis and periodontitis, nor a pharmaceutical kit for oral use comprising the composition of the present invention. Therefore, claims 1-33 are novel in view of this document.

As a result, none of the cited documents disclose all the features of the invention claimed in the present application.

Therefore, claims 1-33 are novel.

Analysis of Inventive Step.

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Claims 1-33 do not involve an inventive step and therefore, do not meet the provisions of PCT Article 33(3).

The technical problem addressed by the invention consists of the need to obtain pharmaceutical compositions that can be used for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth present in the oral cavity, selected from gingivitis and periodontitis, wherein periodontitis is selected from chronic and severe periodontitis.

As a solution to the technical problem addressed in the present invention a pharmaceutical composition is proposed which comprises at least one statin and at least one antiseptic and/or antibacterial agent; a pharmaceutical formulation comprising said composition; the use of this pharmaceutical composition for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth present in the oral cavity, such as gingivitis and periodontitis, selected from chronic and severe periodontitis; and a pharmaceutical kit comprising the composition of the present invention.

Document D1 discloses topical compositions comprising at least one statin as the main active compound for the early prevention or treatment of periodontal disease. This study uses microdilution tests to determine the Minimum Bactericidal Concentration (MBC) (Table 2) and the Minimum Inhibitory Concentration (MIC) (Table 3) for the statins atorvastatin, lovastatin, simvastatin and

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fluvastatin, against important anaerobic periodontal pathogens and commensal bacteria, which are even more relevant in the aetiology of periodontitis than the bacteria indicated in the examples of the application (*Fusobacterium nucleatum* and *Aggregatibacter actinomycetemcomitans*). It was possible to demonstrate that all of them exhibit a bactericidal and bacteriostatic effect. Furthermore, it can be observed even more specifically that for simvastatin, with a MBC of 1 µg/ml (0.001%) and a MIC of 10 µg/ml (0.01%), *Porphyromonas gingivalis* is more sensitive, presenting a relevant inhibitory effect that is sustained over time. Moreover, this study investigated the effects of statins in biofilm formation since the oral biofilm is the crucial extrinsic factor that is responsible for triggering, exacerbating and perpetuating the normal conditions in periodontitis. For this purpose, the impact of statins in the bacteria associated with periodontitis and organised as a multispecies biofilm was investigated. In this process, it was observed that the inhibition of the growth of *P. gingivalis* is the main factor underlying the significant decrease in the total bacterial load observed, due to the fact that the selective removal of this bacterium reestablishes oral homeostasis, stops the progression of periodontitis and prevents alveolar bone loss in animal models. Further, it was possible to establish that patients that are treated with statins can benefit from their anti-inflammatory and immunomodulation properties, which accelerates the return to homeostasis and promotes tissue repair. Likewise, several clinical assays indicate that the topical administration of statins can benefit patients by decreasing inflammation

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and improving bone regeneration. In that respect, this document demonstrated that the antimicrobial activity of statins, and especially of simvastatin targeting *P. gingivalis*, represents a fundamental mechanism underlying the improvement of periodontitis. As a result, this is a relevant study of the effect of statins against *P. gingivalis* since it shows that simvastatin in particular is used in low doses, similarly to the present application, having MBC values of 0.001% (1 µg/ml) and MIC values of 0.01% (10 µg/ml), which correspond to values that are even lower than the 0.02% concentrations used in the statins of the examples stated in the present application. This demonstrates that using the statins disclosed in the formulations of the invention would obtain an expected effect against periodontitis and not a differentiating technical effect.

Document D2 discloses a study to determine the antimicrobial activity or effect of atorvastatin against the primary periodontal pathogens. This study evaluates the antimicrobial effect of atorvastatin against the bacteria *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*, for which Minimum Inhibitory Concentrations (CIM) and Minimum Bactericidal Concentrations (CBM) are used, using the serial dilution method and the culture method, respectively. It was found that both bacteria are sensitive to pure atorvastatin, which also has a potent antimicrobial activity against them. Therefore, it is observed that atorvastatin can be prescribed in patients suffering from periodontal disease. In this regard, in the oral cavity, the bacteria *Aggregatibacter actinomycetemcomitans* and *Porphyromonas*

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gingivalis are considered major pathogens for initiation and progression of the destruction of tooth supporting structures which can increase periodontal conditions (diseases of the hard tissue surrounding the tooth). Thus, this document mentions that atorvastatin exhibits good applicability in the periodontics field as local drug administration agent due to its anti-inflammatory properties, bone regenerative properties and as antimicrobial agent. Moreover, the present MIC and MBC in vitro study demonstrated that atorvastatin can be administered safely and effectively and exhibits a good antimicrobial activity.

Document D3 mentions that periodontitis can cause destruction of the tooth supporting tissues, causing bone and dental loss. Furthermore, it indicates that chronic periodontitis is caused by periodontal pathogenic bacteria such as Porphyromonas gingivalis and Aggregatibacter actinomycetemcomitans. Likewise, this document indicates that the treatment of periodontal disease may involve the use of statins, such as simvastatin. It also indicates that the most used molecules are simvastatin, atorvastatin and lovastatin, and that the use of statins in periodontal disease is due to their anti-inflammatory effect, in addition to stimulating bone formation, angiogenesis and their antimicrobial activity. Furthermore, this document establishes that these drugs are administered in chronic periodontitis as gels, fibres, films, blisters and nanoparticles. The gel stands out as the preferred system to release and transport statins. Moreover, it indicates that, in periodontology, statins have shown a decrease in

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clinical periodontal parameters after 6 months of treatment and that when they are applied topically, they can counteract the inflammation and lead to the regeneration of soft and hard tissues in the treatment of periodontal disease, without the adverse effects of oral administration. It states that statins in gel form are the best option, especially simvastatin in a methylcellulose gel at 1.2% followed by atorvastatin, given that when statins are topically applied, they can counteract the inflammation and lead to the regeneration of soft and hard tissue in the treatment of periodontal disease, without causing the adverse effects of oral administration.

Document D4 discloses an antiseptic pharmaceutical composition used to treat painful lesions of the oral mucosa and ulcerative and inflammatory lesions of different origins and the treatment and/or prevention of oral mucositis and stomatitis. The oral pharmaceutical composition disclosed in this documents comprises at least one antiseptic agent selected from an alcohol derivative selected from ethanol, isopropanol, a paraben derivative, selected from methylparaben, ethylparaben, butylparaben, propylparaben, a peroxide derivative selected from hydrogen peroxide and sodium hypochlorite; an essential oil selected from thymol, menthol, eugenol and methyl salicylate; c. a phenolic antiseptic agent selected from phenol, para-chloro-meta-xyleneol, para-chlorophenol 0.001% to 0.1%, cresol and hexylresorcinol; d. an agent with anti-inflammatory properties selected from camphor 0.006 to 0.05%; xylitol 0.01 to 15% and pharmaceutically acceptable excipients (demineralised

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water), for use thereof in the preparation of a medicine used for the treatment and/or prevention of oral mucositis or stomatitis particularly associated with anticancer therapies.

Document D5 discloses a polyantiseptic antimicrobial pharmaceutical composition for oral use, for the hygiene and treatment of oral diseases of bacterial, mycotic or viral aetiology, consisting of a mixture of hydrogen peroxide, eugenol, natural camphor, xylitol, and excipients (water), among other components. The formulation is used to deodorise, disinfect, astringe and soothe inflammation of the oral area. This composition prevents gingivitis and periodontal diseases, among other diseases, because it effectively acts against the bacteria *Porphyromonas gingivalis*. Furthermore, this formulation is in the form of a mouthwash, gel or toothpaste.

Therefore, claim 1 does not have any features providing an inventive step since the disclosure in documents D1, D2 or D3 in combination with that which is indicated in document D4, leads to a pharmaceutical composition comprising at least one statin and at least one antiseptic and/or antibacterial agent, such as that which is disclosed in claim 1. Moreover, the specific selection of a fat-soluble statin such as lovastatin, simvastatin, atorvastatin and pitavastatin or of a water-soluble statin such as pravastatin, fluvastatin and rosuvastatin in low concentrations such as that which is disclosed in claims 4-8, does not contribute an inventive step to the present invention, since the election of both types of

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statins, specifically of atorvastatin, lovastatin, simvastatin and fluvastatin, and the use of low concentrations such as those disclosed for simvastatin of 0.001% to achieve a bacteriostatic effect and 0.01% to achieve a bactericidal effect, is also disclosed for the topical compositions mentioned in document D1. Moreover, the selection of an oxidant antiseptic and/or antibacterial agent which is hydrogen peroxide and sodium hypochlorite, which further comprises at least one facilitating auxiliary agent that is a phenol-derived preservative such as phenol, parachlorophenol, an alkylparaben such as methylparaben, ethylparaben, propylparaben, butylparaben, an essential oil such as eugenol and camphor, and a wetting agent such as xylitol, such as that which is disclosed in claims 2, 3 and 9-23, do not confer an inventive step to the present application since their use and low concentrations are already disclosed in the oral pharmaceutical composition of document D4 comprising, among other components, antimicrobial or antiseptic agents such as hydrogen peroxide, in a concentration between 0.001% to 1% w/w, and sodium hypochlorite, which despite failing to disclose the concentrations being used, said selection of amounts is within the usual practice of a person skilled in the art when testing different concentrations until the best formulation that achieves the expected effect is reached, eugenol in a concentration between 0.005% to 0.04% w/w, a phenolic antiseptic agent such as phenol and para-chlorophenol in a concentration between 0.001% to 0.1% w/w and an agent with anti-inflammatory properties selected from camphor in a concentration between 0.006% to 0.05% w/w. Likewise, the selection of the wetting

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agent xylitol in low concentrations does not confer an inventive step to the present application since the oral pharmaceutical composition mentioned in document D4 also mentions that it comprises xylitol, among other components, in a concentration between 0.01% to 15% w/w. Moreover, the indications with respect to the fact that the composition must have a diluent as at least one facilitating auxiliary agent which is purified water and that it further comprises a pH regulator that is a bicarbonate buffer and flavourings, sweeteners or a mixture thereof, which is disclosed in claims 24-28, does not contribute a differentiating technical feature to the present invention. This is due to the fact that it may be part of the typical selection for a person skilled in the art being prompted to obtain a better formulation for their invention. Furthermore, based on document D4, it is clear that this composition can be in the form of mouthwash, as disclosed in claim 29. Additionally, based on the disclosures in documents D1, D2 and D3, it can be established that the formulation would be useful for preventing and/or treating diseases in the soft and hard tissues surrounding the tooth present in the oral cavity such as gingivitis and periodontitis and based on document D4 that it would be useful for treating diseases of the soft tissues in the oral cavity such as painful lesions in the oral mucosa, as disclosed in claims 30-32. Moreover, obtaining a pharmaceutical kit comprising a composition such as that which is disclosed in claim 1 that is not inventive does not confer an inventive step to claim 33 of the present application.

In a similar analysis, based on the disclosures in

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documents D1, D2 or D3 in combination with the disclosure in document D5, a pharmaceutical composition can be obtained comprising at least one statin and an antiseptic and/or antibacterial agent, such as that which is disclosed in claim 1. Moreover, the specific selection of a fat-soluble statin such as lovastatin, simvastatin, atorvastatin and pitavastatin or of a water-soluble statin such as pravastatin, fluvastatin and rosuvastatin in low concentrations such as that which is disclosed in claims 4-8, does not contribute an inventive step to the present invention, since the selection of both types of statins, specifically of atorvastatin, lovastatin, simvastatin and fluvastatin, and the use of low concentrations such as those disclosed for simvastatin of 0.001% to achieve a bacteriostatic effect and 0.01% to achieve a bactericidal effect, is also disclosed for the topical compositions mentioned in document D1. Moreover, the selection of an oxidant antiseptic and/or antibacterial agent which is hydrogen peroxide, which further comprises at least one facilitating auxiliary agent that is an essential oil such as eugenol and camphor, and a wetting agent such as xylitol, such as that which is disclosed in claims 2, 3, 9, 10 and 18-23, do not confer an inventive step to the present invention since their use and low concentrations are already disclosed in the oral pharmaceutical composition of document D5 comprising among other components, an antimicrobial or antiseptic agent such as hydrogen peroxide in a concentration of 0.1% w/w, eugenol in a concentration of 0.01% w/w, and an agent with anti-inflammatory properties selected from camphor in a concentration between 0.001% to 0.007% w/w. Likewise, the

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selection of the wetting agent xylitol in low concentrations does not confer an inventive step to the present application since the oral pharmaceutical composition mentioned in document D5 also discloses that it comprises, among other components, xylitol in a concentration between 2% and 7% w/w. Moreover, although these documents are not directly detrimental to claim 11, because documents D1, D2 and D3 only disclose compositions comprising statins and document D5 does not mention the presence of sodium hypochlorite, the use of said component is known due to its antiseptic and/or bactericidal action so the selection thereof could have been a trivial matter for a person skilled in the art to form part of the formulation indicated, and furthermore, its selection does not confer any differentiating technical feature to the formulation obtained. This means that said claim does not involve an inventive step either. Moreover, the indication with respect to the fact that the composition of the invention must a diluent as at least one facilitating auxiliary agent which is purified water and that it further comprises a pH regulator that is a bicarbonate buffer and flavourings, sweeteners or a mixture thereof, which is disclosed in claims 24-28 does not contribute a differentiating technical feature to the present invention. This is due to the fact that it may be part of the typical selection for a person skilled in the art being prompted to obtain a better formulation for their invention. Furthermore, based on document D5, it is clear that this composition can be in the form of mouthwash, gel or toothpaste, as disclosed in claim 29. Moreover, based on the disclosures in documents D1, D2 and D3, it can be established that

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Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

the formulation would be useful for preventing and/or treating diseases in the soft and hard tissues surrounding the tooth present in the oral cavity such as gingivitis and periodontitis and based on document D5 that it would be useful for treating gingivitis and periodontal diseases, as disclosed in claims 30-32. Moreover, obtaining a pharmaceutical kit comprising a composition such as that which is disclosed in claim 1 that is not inventive does not confer an inventive step to claim 33 of the present application.

Therefore, it would be obvious for the person skilled in the art to arrive at the subject matter included in claims 1-33 as a result of that which is disclosed in document D1-D5, according to the previously mentioned combination, since based on the teachings delivered in these documents, they would be prompted to low doses of statins together with antiseptic and/or antibacterial agents include in a formulation, with the clear expectation of being able to obtain pharmaceutical compositions that are effective for preventing and/or treating diseases of the soft and hard tissues present in the oral cavity, especially for preventing and/or treating gingivitis and periodontitis.

As a result, documents D1-D5, according to the aforementioned combination of documents, show that claims 1-33 do not involve an inventive step.

Analysis of Industrial Applicability.

The invention as defined in claims 1-33 meets the

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requirement of PCT Article 33(4) in respect of industrial applicability.

Box No. VIII **Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 22 and 31 of the set of claims do not comply with PCT Article 6.

Claim 22 is incorrectly dependent on claim 19, since claim 22 relates to a composition according to claim 19 CHARACTERISED in that the wetting agent is xylitol, whereas claim 19 relates to a composition CHARACTERISED by a facilitating auxiliary agent that is an essential oil that is selected from eugenol, camphor and a mixture thereof. The correct form would be for claim 22 to depend on claim 21 which in effect relates to a composition wherein the facilitating auxiliary agent is a wetting agent. Since the dependency of this claim is incorrect, claim 22 shall be considered dependent on claim 21 for search and analysis purposes of the present application.

Claim 31 is incorrectly dependent on claim 29, since claim 31 relates to the use of a composition according to claim 29 CHARACTERISED in that the disease of the soft and hard tissues surrounding the tooth is selected from gingivitis and periodontitis, whereas claim 29 relates to a pharmaceutical formulation CHARACTERISED in that it comprises a composition according to claim 1 wherein said formulation is selected from toothpaste, gel, mouthwash, dental floss, tablets for dissolving inside the mouth and controlled-release intraoral elements and/or devices such as capsules with microparticles and nanoparticles. The correct form would be for claim 31 to be dependent on claim 30 which relates to the use of a composition

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CHARACTERISED in that it is used to prepare a medicine for preventing and/or treating diseases of the soft and hard tissues surrounding the tooth present in the oral cavity. Since the dependency of this claim is incorrect, claim 31 shall be considered dependent on claim 30 for search and analysis of the present application.