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Datasheet for the decision of 11 April 2024

Case Number: T 1959/21 - 3.3.07

Application Number: 09002569.3

Publication Number: 2186507

IPC: A61K9/00, A61K31/465

Language of the proceedings: EN

Title of invention:
A liquid pharmaceutical formulation comprising nicotine for the administration to the oral cavity

Patent Proprietor:
McNeil AB

Opponents:
Fertin Pharma A/S
ALIUD PHARMA GmbH

Headword:
Liquid nicotine formulation II/MCNEIL AB

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - obvious improvement

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Case Number: T 1959/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 April 2024

Appellant: (Patent Proprietor)	McNeil AB P.O.Box 941 251 09 Helsingborg (SE)
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Respondent: (Opponent 1)	Fertin Pharma A/S Dandyvej 19 DK-7100 Vejle (DK)
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Respondent: (Opponent 2)	ALIUD PHARMA GmbH Gottlieb-Daimler-Straße 19 89150 Laichingen (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 October 2021 revoking European patent No. 2186507 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 2 186 507 ("the patent") was granted on the basis of sixteen claims.

Claim 1 as granted defined:

"A pharmaceutical formulation for use in the treatment of addiction to tobacco or nicotine comprising nicotine and characterized in that
(i) the nicotine is present as a free nicotine base;
(ii) the pharmaceutical formulation is a buffered alkaline liquid formulation for administration to the oral cavity of a subject by spraying, dropping or pipetting; and in that
(iii) the nicotine is co-administered with a buffering agent."

II. The patent was opposed on the grounds that its subject-matter lacked an inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the earlier application as filed.

The decision of the opposition division to revoke the patent announced during the oral proceedings of 13 October 2017 was set aside in the decision on appeal T 534/18. In that decision the Board concluded that the patent as granted did not contain subject-matter extending beyond the content of the (parent) application as originally filed and remitted the case to the opposition division for examination of the further grounds of opposition.

Following the remittal a notice of intervention under Article 105 EPC was filed.

The present appeal was filed by the patent proprietor against the subsequent decision of the opposition division to revoke the patent. The decision was based on the patent as granted (main request) and auxiliary requests 1-6 as filed on 17 April 2018.

In its decision the opposition division cited *inter alia* the following documents:

D1: US 6,024,297
D2: GB 2 255 892 A
D4: Journal of Analytical Toxicology, 2001, 25, 15-24
D7: J. Serb.Chem. Soc., 2014, 79(7) 829-842
D8: Study Report Gunilla Sjöstedt dated 28 October 2010, "In-house study, pH measurement Oromucosal Nicotine Spray with Buffer (ONSB) 0.5 mg/spray and Oromucosal Nicotine Spray no Buffer (ONSB) 0.5 mg/spray"
D14: Tobacco Control, 1997, 6, 219-225
D16: Archives of Oral Biology, 2000, 45, 1-12

The opposition division arrived at the following conclusions:

(a) The intervention under Article 105 EPC complied with the requirements for admittance.

(b) Taking account of the experimental results reported in the patent, which showed that nicotine from formulations as defined in the claims is readily absorbed into the bloodstream and provides for a reduction of the urge to smoke, the patent as

granted complied with the requirement of sufficient disclosure.

(c) The patent provided formulations which allowed for a rapid uptake of nicotine. Document D1 represented the closest prior art describing liquid formulations comprising nicotine for administration in the oral cavity by spraying.

The formulation claimed in the patent differed from the formulations described in document D1 in the presence of a buffer. The experimental data reported in document D8 showed that the pH of the saliva increases faster and to a higher level using a nicotine solution with an alkaline buffer as compared when using an unbuffered nicotine solution. As indicated in for instance document D2 higher pH values favoured faster and more complete buccal absorption of nicotine. The problem credibly solved was therefore the provision of an improved product for use in the treatment of nicotine/ tobacco addiction.

The formulation of nicotine in a liquid composition with an alkaline buffer as defined in claim 1 of the patent as granted was an obvious solution to the identified objective technical problem, because it was well known from *inter alia* documents D2, D4 and D14 that the buccal absorption of nicotine is promoted by alkalinisation of the mouth. Claim 1 of the main request did therefore not involve an inventive step.

(d) Auxiliary requests 1-6 did not comply with the requirement of inventive step for the same reasons as the main request.

III. With the statement of grounds of appeal the patent proprietor upheld only the main request relating to the patent as granted.

IV. In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that the patent as granted did not comply with the requirement of inventive step.

V. Oral proceedings were held on 11 April 2024.

VI. The arguments of the patent proprietor (appellant) relevant to the present decision are summarized as follows:

The experimental results reported in the patent demonstrated that the claimed liquid formulations provided similar rapid absorption of nicotine as from smoking.

Document D1 represented the most suitable starting point in the prior art with respect to the claimed liquid formulations, because document D1 also relates to liquid formulations for buccal administration in which the nicotine is already present in dissolved form, be it without the buffer as defined in the claims of the patent.

The additional experimental results reported in document D8 demonstrated a more pronounced increase of the pH of the saliva to above 8.0 from a liquid nicotine formulation comprising a buffer than from such a composition without a buffer, which left the pH of the saliva below 7.5. As explained in paragraph [0049] of the patent nicotine is faster

absorbed at the higher pH level. Document D8 therefore substantiated an advantage of the claimed buffered formulations over the liquid composition of document D1.

The objective technical problem was therefore the provision of an improved product for use in treating nicotine/tobacco addiction which provides similar rapid absorption of nicotine as from smoking.

It was not obvious to solve this problem by including a buffer in the liquid composition of document D1.

Conventional solid nicotine formulations as for instance described in documents of D2 and D14 (tablets, lozenges, chewing gum, capsules) still required the dissolution of the nicotine after administration and could therefore not provide any suggestion for a relevant modification of the liquid formulation of document D1.

The saliva represented the transfer medium for the absorption of the nicotine by the buccal mucosa from these solid compositions, which required an alkaline buffer to provide an adequately high pH level to allow effective buccal absorption. In contrast and as evidenced by document D7 the dissolution of nicotine in water directly provides an alkaline liquid formulation comprising the dissolved nicotine in the form of the free base, which is readily absorbed by the buccal mucosa. As demonstrated in example 11 of the patent the nicotine provides itself buffer capacity to such a solution.

Moreover, the administration of the solid formulations provokes stimulated saliva which has according to documents D4 and D16 greater volume and higher buffering capacity than the unstimulated saliva which is present in the buccal cavity when a liquid formulation of document D1 is administered.

Without the benefit of hindsight the prior art therefore provided the skilled person with no motivation towards the claimed solution involving the addition of a buffer to the liquid composition of document D1.

VII. The arguments of the intervener (respondent) relevant to the present decision are summarised as follows:

The claimed formulation differed from the liquid formulations comprising nicotine to be administered in the form of a mouth spray as described in document D1 only in the presence of an alkaline buffer.

As evidenced by document D14 it was common knowledge that nicotine has a pKa of 8.02 and that the buccal absorption rate of nicotine therefore increases at higher pH values. It was further common knowledge that the pH of whole mouth saliva varies around 7 and that the saliva comprises bicarbonate which provides buffer capacity. The skilled person would therefore realize that upon contact with the saliva the nicotine in the sprayed liquid of document D1 will as a matter of course to some extent be protonated, which negatively affects the rate of its buccal absorbance. It was therefore obvious for the skilled person to include an

alkaline buffer in the liquid nicotine formulation of document D1 to keep the nicotine in the form of the absorbable free base in the buccal environment and to thereby enhance the buccal absorption rate of the nicotine, especially since buffers had already been used in solid compositions for buccal administration of nicotine.

VIII. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted (main request).

IX. The respondent-intervener requested that the appeal be dismissed.

X. The respondent-opponent did not file any observation or request during the appeal proceedings.

Reasons for the Decision

1. The claimed invention as described in the patent

The patent describes the purpose of the claimed liquid formulations comprising nicotine in the form of the free base in buffered alkaline liquid as the provision of fast relief to nicotine craving by rapid transmucosal uptake of nicotine (see paragraphs [0024]-[0029] and [0038]).

The patent presents in this context experimental results which indicate that

- a sprayed formulation according to claim 1 with 3.5 mg nicotine reaches maximum plasma levels of about 7 ng/ml within few minutes, whereas a sublingual

tablet with 4 mg nicotine only reaches such plasma levels after more than 30 minutes (see Figure 1)

- an alkaline sprayed formulation according to claim 1 with a pH of 8.5 provides for higher and more rapidly achieved plasma levels than sprayed formulations which are buffered at a pH of 6 or 7 (see Figure 2)

- smoking a "light" cigarette achieves a peak plasma level of above 12 ng/ml of nicotine within 10 minutes, whereas a Nicorette gum with a dose of 4 mg nicotine only reaches a maximum level of about 9 ng/ml after more than 30 minutes (see Figure 3)

- a sprayed formulation according to claim 1 with 3.5 mg nicotine provides for a fast "craving" reduction in smoking volunteers (-50% in 2 minutes) as compared to a sublingual tablet with 4 mg nicotine (-50% after more than 10 minutes) (see Figure 4).

2. Objective technical problem

Document D1 describes liquid nicotine formulations for assisting smoking cessation which are sprayed in the oral cavity for direct absorption by the buccal mucosa (see D1, claim 1 and column 4, lines 3-11 and lines 33-39). The person wishing to give up smoking who feels the need for a cigarette is according to document D1 thereby provided a suitable amount of the liquid containing the nicotine (see D1, column 5, lines 43-49).

The claimed formulation differs from the liquid composition described in document D1 in the presence of a buffer.

It was not in dispute that the presence of the buffer in the liquid formulation allows, as demonstrated by the results reported in document D8 (see pages 6 and 7), for a more pronounced increase in the pH of the saliva and that this more pronounced increase favours the rapid buccal absorption of the contained nicotine. The parties thus agreed that starting from document D1 the objective technical problem may be seen in the provision of an improved product.

3. Assessment of the solution

3.1 Common general knowledge

Document D14 reviews the evidence on the relation between the absorption of nicotine across the mucosal lining of the oral cavity and the pH of smokeless tobacco products (see title; see page 220, lines 60-64).

In the section under the heading "Background" document D14 indicates that the speed of absorption of nicotine is a major determinant of its psychoactive effects. The document explains that nicotine has a pKa of 8.02 and that increasing the pH transforms nicotine in the un-ionized free base form, which is more readily absorbed across physiological membranes than the ionized acid form. According to document D14 even the neutral pH oral environment, in which the bicarbonate in the saliva provides buffer capacity, allows for the eventual absorption of the free base of nicotine. However, the effect of an alkaline pH is the increased rate of absorption of the nicotine and therefore the enhancement of its psychoactive properties (see D14,

page 219, right column, line 23 to page 220, left column, line 32).

The patent proprietor did not contest that this background information in document D14 represents common general knowledge.

3.2 Faced with the identified objective technical problem the skilled person recognizes that by spraying the liquid nicotine composition in the buccal cavity as described in document D1 the nicotine comes in contact with saliva. On the basis of the above mentioned common general knowledge represented in document D14 the skilled person would realize that the neutral pH and buffering capacity of saliva leads to protonation of at least some part of the nicotine from the unbuffered formulation of document D1 and that the rate of the absorption of the nicotine and consequentially its intended effect is thereby at least to some extent impeded.

It was already known to improve the buccal absorption rate of nicotine from solid formulations by including an alkaline buffer. In this context document D14 specifically refers to a study involving nicotine replacement products in the form of gelatine capsules for buccal application of nicotine. According to the results of this study an increase in the concentration of the alkaline buffer in a capsule with 4 mg nicotine raised the peak nicotine plasma levels from 4-10 ng/ml to 10-15 ng/ml (see D14, page 223, paragraph bridging left and right column).

The skilled person had therefore a reasonable expectation that the nicotine absorption from the formulation of document D1 would also be improved by

including a buffer to counter the effect of the pH of the saliva on the nicotine absorption.

3.3 The patent proprietor argued that the nicotine in the liquid compositions of document D1 was already in the dissolved absorbable form of the free base, which itself provided buffer capacity to the composition, whereas the known solid compositions required the saliva as the dissolving transfer medium. In this context the proprietor further argued that the liquid compositions of document D1 only come in contact with unstimulated saliva, which has according to documents D4 and D16 significantly lower buffer capacity and is produced at a lower rate compared to the stimulated saliva that dissolves the nicotine from solid compositions. The skilled person had therefore no motivation to include a buffer in the liquid compositions of document D1.

The Board notes that documents D4 and D16 indeed report lower buffer capacities and flow rates for unstimulated saliva as compared to stimulated saliva (see D4, page 22, Table V; see D16, abstract). However, these documents still confirm the neutral pH and the buffering capacity of the saliva in the oral cavity, including the unstimulated saliva. Due to the neutral pH and buffering capacity of the saliva it was to be expected that without any additional buffer the nicotine, which is in accordance with document D1 only administered in microgram amounts, would upon contact with the neutral unstimulated saliva at least to some extent be protonated to the ionized form and thereby be impeded in its rate of absorption. The skilled person would therefore be motivated to add an alkaline buffer to the formulation of document D1 to preserve the

nicotine in the free base form and thereby improve the absorption rate of the nicotine.

3.4 Accordingly, the Board concludes that the subject-matter of the main and only request does not involve an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated