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Case Number: T 2645/16 - 3.3.07

Application Number: 06809154.5

Publication Number: 1945186

IPC: A61K9/20, A61K31/197, A61P25/00

Language of the proceedings: EN

Title of invention:
SOLID ORAL PHARMACEUTICAL COMPOSITIONS FOR ONCE DAILY DOSING CONTAINING PREGABALIN, A MATRIX FORMING AGENT AND A SWELLING AGENT

Patent Proprietor:
Upjohn US 1 LLC

Opponent:
Strawman Limited

Headword:
Solid oral pharmaceutical compositions containing pregabalin/ UPJOHN

Relevant legal provisions:
RPBA Art. 12(4)
EPC Art. 114(2), 56

Keyword:
Admission of D14-D18 (No)
Admission of D19-D22 (Yes)
Main request - Inventive step (Yes)

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Case Number: T 2645/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 March 2021

Appellant: (Opponent)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Patent Proprietor)	Upjohn US 1 LLC 235 East 42nd Street New York NY 10017 (US)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 13 October 2016 rejecting the opposition filed against European patent No. 1945186 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 1 945 186 was granted on the basis of a set of 12 claims.

Independent claim 1 as granted read as follows:

> 1. A pharmaceutical composition comprising an active pharmaceutical ingredient and excipients, the active pharmaceutical ingredient comprising pregabalin, or a pharmaceutically acceptable complex, salt, solvate or hydrate thereof, and the excipients comprising a matrix forming agent and a swelling agent, the matrix forming agent comprising polyvinyl acetate and polyvinylpyrrolidone, and the swelling agent comprising cross-linked polyvinylpyrrolidone, wherein the pharmaceutical composition is adapted for once-daily oral dosing.

II. An opposition was filed against the granted patent on the grounds that its subject-matter lacked inventive step.

III. The present appeal lies from the decision of the opposition division to reject the opposition (Article 101(2) EPC).

IV. The documents cited during the opposition proceedings included the following:

D1: Frampton & Scott, Drugs 2004, 64(24), 2813-2820
D2: Chawla et al., Pharmaceutical Technology July 2003, 50-65

D3: Hou et al., Critical Rev in Therapeutic Drug Carrier Systems 2003, 20(6), 461-497
D6: Fussnegger, Internet Publication from June 2003
D7: US 6635279 B2
D8: Draganoiu et al., Pharm Ind 2001, 63(6), 624-629
D17: Arora S et al. AAPS PharmSciTech 2005 6(3) Article 47 (19 October 2005)

V. According to the decision under appeal, documents D14 to D18 were not admitted into the opposition proceedings, since late-filed by the opponent and without any justification for the late filing. The documents were furthermore considered to be not *prima facie* relevant, at least not more relevant than the documents already on file.

As regards inventive step, document D1 was considered to represent the closest prior art document. D1 did not disclose a specific dosage form of pregabalin. The objective technical problem was seen in the provision of a pharmaceutical composition comprising pregabalin adapted for once-daily oral dosing. The claimed solution was inventive.

VI. The opponent (hereinafter the appellant) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal dated 22 February 2017, the appellant submitted the following items of evidence:
D19: Chapter 20 of “Pharmaceutics: The Science of Dosage Form Design” (Aulton”)
D20: The Scientific Discussion from the EMEA approval of pregabalin (December 2004)
D21: Ben-Menachem, Epilepsia (2004),45(Suppl6), 13-18
D22: Jezyk et al, Pharm. Research, 1999, 16(4), 519-526

VIII. With a letter dated 6 July 2017, the patent proprietor (hereinafter the respondent) filed auxiliary requests 1 and 2 corresponding respectively to auxiliary requests 1-2 filed previously in the opposition proceedings. It also requested that documents D14-D18 and D19-D22 not be admitted into the proceedings.

IX. On 20 February 2020 the Board issued a communication indicating, in particular, that the claimed invention appeared to be inventive.

X. Oral proceedings took place on 30 March 2021 by videoconference.

XI. The arguments of the appellant may be summarised as follows:

Admission of D14-D18 into the proceedings

D14-D18 clearly addressed a point raised in the preliminary opinion of the opposition division, namely that D1 disclosed the narrow window of absorption of pregabalin. They were submitted to specifically address this latter question and were clearly relevant to the appellant's inventive step argument as they explained the conventional use of cross-linked swelling agents in controlled release compositions, especially those designed to be retained in the stomach. D14-D18 were submitted within the time limit set by the opposition division and were of direct relevance, and should have been admitted into the proceedings.

Admission of D19-D22 into the proceedings

Documents D19-D22 were submitted to support the that knowledge of the narrow window of absorption of pregabalin was known from D1. They were filed in response to the decision of the opposition division, and the appeal was the first opportunity to submit these documents.

Main request - Inventive step

Starting from D1, there was a motivation to develop a once-daily composition for administering pregabalin. D1 disclosed that all clinical trials had involved administering pregabalin two or three times a day. Motivation to adapt the multiple daily dosage to a single daily composition therefore existed.

D1 disclosed that pregabalin was an amino acid analogue like the related drug gabapentin, and had "rapid absorption" after oral administration, with a C_{max} of 1.3 h and rapid elimination half-life. This was an evidence that pregabalin had a narrow window of absorption under the model shown in Figure 2 of D2. This was confirmed by the disclosure of D19, D20, D21 and D22, which were all relevant as they disclosed the role of intestinal amino-acid carriers in the rapid absorption of pregabalin. The person skilled in the art would have known that pregabalin was preferably absorbed in the small intestine by an amino acid transport system and displayed a narrow window of absorption and therefore that a gastroretentive drug delivery system (GRDDS) would have been considered as preferable for the development of a once-daily pregabalin composition. The development of such a GRDDS was a routine development procedure as being a standard solution for the "narrow absorption window" drugs. Textbooks such as D19 and reviews such as D2, D3 and

D17 confirmed that GRDDS represented the best method for preparing a once-daily composition.

Claim 1 included no feature that characterised the once-daily composition as being a GRDDS, and only examples 24 and 30 were shown explicitly to be GRDDS, in view of the modifications of the tablets dimensions by swelling shown in Table 12. The skilled person could not exclude that the other examples related to simple sustained release dosage forms. A simple addition of a matrix polymer and a swelling polymer was a common solution in the latter case. The invention involved the routine use of a known polymer mixture (Kollidon® SR, mixture of polyvinyl acetate and polyvinyl pyrrolidone). The modification involved the addition of a swelling agent in the form of a cross-linked polymer. D6 and D7 showed the use of Kollidon® SR in GRDDS or controlled release technology, and the addition of a swelling polymer was also obvious. The person skilled in the art, when considering development of such Kollidon® SR as a conventional controlled release composition or a GRDDS would have applied routine experimentation and added cross linked PVP to speed up swelling of the tablet by enhancing the penetration and rate of absorption of water on administration; this was shown by D14 and D18. The claimed solution could not be inventive.

XII. The arguments of the respondent may be summarised as follows

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Admission of D14-D18 into the proceedings

Documents D14 to D18 were late submitted in the opposition proceedings. The decision of the opposition division referred correctly to the lack of *prima facie*

relevance of the documents and the failure of the appellant to explain the late filing.

In the appeal proceedings, the appellant had not provided any further justification for the late submission of the documents other than that they addressed a point raised in the preliminary opinion of the opposition division, without explaining what particular point was addressed and how the information included in the documents was relevant in view of the documents already on file. It remained completely unclear why the documents were considered by the appellant to have any relevance.

Admission of D19-D22 into the proceedings

The submission of these documents might be an attempt to address the issue of the "narrow absorption window". However, they could have been submitted during the opposition proceedings.

Main request - inventive step

D1 was the closest prior art document. The fact that pregabalin had a limited window of absorption in the GI tract was not derivable from D1 or any other document cited. D1 only reported that pregabalin was rapidly and efficiently absorbed following oral administration.

Moreover, the skilled person would not have been motivated to pursue a gastric-retained system, but would have preferred to pursue a conventional controlled-release formulation since success was more likely with such a formulation. D2 and D3 actually taught that GRDDS was, at the relevant time, only an emerging field of research.

Even if a GRDDS were to be pursued, there was no clear teaching that would lead the skilled person to the formulation as claimed. There had been no motivation to choose a polyvinyl acetate matrix over an HPMC matrix, which was the first choice. Finally, even if a polyvinyl acetate matrix were to be selected, there would have been no motivation to modify it in any way, let alone by inclusion of cross-linked polyvinylpyrrolidone. The formulations of D6 were binary combinations of an active ingredient and a polyvinyl acetate matrix (Kollidon). However, nothing in this document suggested that it was desirable, or even possible, to use a further excipient to modify the properties of the tablet. The data presented both in the application as filed and in D13 showed that the tablets according to the claims functioned as swelling and floating controlled release dosage forms, and that they maintained these properties even when compressed with a force that is high enough to provide hard tablets capable of withstanding typical manufacturing processes.

XIII. Requests

The appellant requested that the decision under appeal be set aside and the patent be revoked.

The respondent requested that the appeal be dismissed, alternatively that the decision under appeal be set aside and the patent be maintained according to one of the sets of claims filed as auxiliary requests 1 and 2 with letter of 6 July 2017.

The respondent also requested that documents D14-D18 and D19-D22 not be admitted into the proceedings.

Reasons for the Decision

1. Admission of documents D14-D18 into the proceedings

1.1 These documents were filed during the opposition proceedings after the expiry of the 9 month period provided in Art 99(1) EPC, but within the time limit set by the opposition division under Rule 116(1) EPC. According to the appellant, the documents were submitted in support of its arguments with regard to the assessment of inventive step, in particular whether the skilled person would prepare a composition as claimed.

The opposition division did not admit said documents into the opposition proceedings and based its decision on the absence of justification by the opponent for the late filing of these documents, and on the fact that said documents were *prima facie* considered to be not relevant, at least not more relevant than the documents on file.

1.2 The Board notes that none of documents D14-D18 deals with dosage forms comprising pregabalin as active substance or with the composition or excipient system of claim 1 of the main request. These documents indeed do not appear *prima facie* relevant for the assessment of inventive step, this all the more since several documents of a higher relevance were already on file. Documents relating generally to gastric retention drug delivery systems (GRDDS), such as *inter alia* D2 or D3, or relating more specifically to GRDDS or compositions comprising the claimed excipients, such as D6-D8, were indeed already on file, and were submitted and

discussed by the appellant in the opposition proceedings.

Hence, the Board sees no point in submitting additional and less relevant documents on specific issues already well supported.

1.3 Consequently, in not admitting D14-D18 into the opposition proceedings, the opposition division exerted correctly and reasonably its discretionary power in accordance with the right principles.

1.4 The Board concurs with the opposition division's view and accordingly also sees no reason to admit these documents into the proceedings (Article 12(4) RPBA 2007 and Article 114(2) EPC).

2. Admission of documents D19-D22 into the proceedings

2.1 Documents D19-D22 were filed with the statement of grounds of appeal and thus at the very beginning of the appeal proceedings.

They relate to an issue which has always been a point of discussion before the opposition division and which is still relevant, namely the possible knowledge at the filing date of the contested patent of a narrow gastro-intestinal absorption window of pregabalin.

2.2 In view of the file history, it appears that such documents could not have been filed earlier in the opposition proceedings. The opposition division stated in its preliminary opinion with regard to pregabalin and gabapentin, that "it was also known that both compounds had a limited absorption window, as it is said in paragraph [0004] of the patent" (see point 7.

of the preliminary opinion). The decision of the opposition division mentions however that it could not be deduced from the closest prior art D1 that pregabalin had such a "narrow window absorption".

2.3 In view of the preliminary opinion of the opposition division, it is therefore comprehensible that the appellant did not find necessary to submit documents on this specific point. The appeal is therefore the first opportunity to address this point in response to the argumentation of the opposition division and these documents might be of crucial importance in the discussion on inventive step.

2.4 Consequently, the documents D19-D22 are admitted in the appeal proceedings (Article 12(4) RPBA 2007).

3. Main request - inventive step

3.1 The invention relates to solid pharmaceutical compositions containing pregabalin suitable for once daily oral dosing.

3.2 As agreed by all parties, the closest prior art is D1, which is the only document on file relating to pregabalin and discloses its pharmacodynamic and pharmacokinetic properties. D1 (see page 2813) discloses an oral administration of pregabalin with a frequency of 2 or 3 times daily for a recommended dosage of 150-600mg/day, but does not disclose any specific dosage form of pregabalin.

With regard to the pharmacokinetic properties of pregabalin, D1 mentions a rapid absorption with a C_{max} of 1.3 hours, a short half life of 4.6-6.8 hours, and a

very high bioavailability of 90% (see Table on page 2813 and page 2815).

3.3 The problem to be solved is the one also considered by the opposition division in its decision, namely the provision of a pharmaceutical composition suitable for once daily administration.

The appellant also agreed with the formulation of the problem.

3.4 As a solution to this problem, claim 1 of the main request proposes a composition with excipients comprising a matrix forming agent and a swelling agent, the matrix forming agent comprising polyvinyl acetate and polyvinylpyrrolidone, and the swelling agent comprising cross-linked polyvinylpyrrolidone,

3.5 Examples 24-28 and 30 of the contested patent disclose compositions comprising *inter alia* pregabalin, Kollidon® SR (polyvinyl acetate and polyvinylpyrrolidone) and Plasdone® XL (cross-linked polyvinypyrrolidone). Said compositions show a 24 hours release, as illustrated in Table 11 of the patent, which demonstrates that the claimed compositions are suitable for a once-daily administration.

Table 12 highlights also the swelling properties of the compositions 24 and 30 as a function of time, and proves that said compositions expand their dimensions over a specific size necessary for their retention in the stomach (see par. [0061]), in particular within the 6 first hours of immersion in an aqueous solution. This size expansion is a clear evidence that the dosage form will be retained in the stomach by size exclusion and confirms that said dosage forms are indeed GRDDS.

Moreover, contrary to what was argued by the appellant, there is no reason to doubt that the other compositions 25-28 do not exhibit the same expansion properties, given the similarity of the compositions with the compositions of examples 24 and 30.

Consequently, there is sufficient evidence supporting the alleged effect. The Board is convinced that the claimed compositions present a 24 hour release and expansion properties characterising GRDDS, so that the problem of providing a pharmaceutical composition suitable for once daily administration is credibly solved.

3.6 The question remaining is whether the skilled person, starting from the teaching of D1, would arrive at the subject-matter of claim 1 of the main request in an obvious manner in order to solve the problem posed.

3.6.1 According to the appellant, the existence of a "narrow gastrointestinal absorption window" of pregabalin was known from D1 and was also derivable from the teachings of D2 and D19-D22. Furthermore, in view of this knowledge, the use of a GRDDS was an immediate and obvious solution, in particular in view of D2, D3, D19 and D6-D8.

These two points are essential with regard to the obviousness of the solution and need to be assessed.

3.6.2 Document D2 was mentioned by the appellant to illustrate what is meant by "narrow absorption window" and why pregabalin had such "narrow absorption window".

According to D2, an important requisite for the successful performance of oral controlled-release drug delivery systems (CRDDS)is that a drug should have good absorption throughout the gastrointestinal tract (GIT) preferably by passive diffusion. Some drugs are absorbed in a particular portion of the GIT only or are absorbed to a different extent in various segments of the GIT (see pages 51 and 52). Drugs absorbed by active and facilitated mechanisms show higher regional specificity because of the prevalence of these mechanisms in only certain regions of the GIT (see D2, page 52, right hand col., first par.) GRDDS can improve the controlled delivery of drugs that have an absorption window by continuously releasing the drug for a prolonged period of time before it reaches its absorption site (see page 52, right hand column, "Gastroretentive drug delivery systems"). This is illustrated by following Figure 2 of D2.

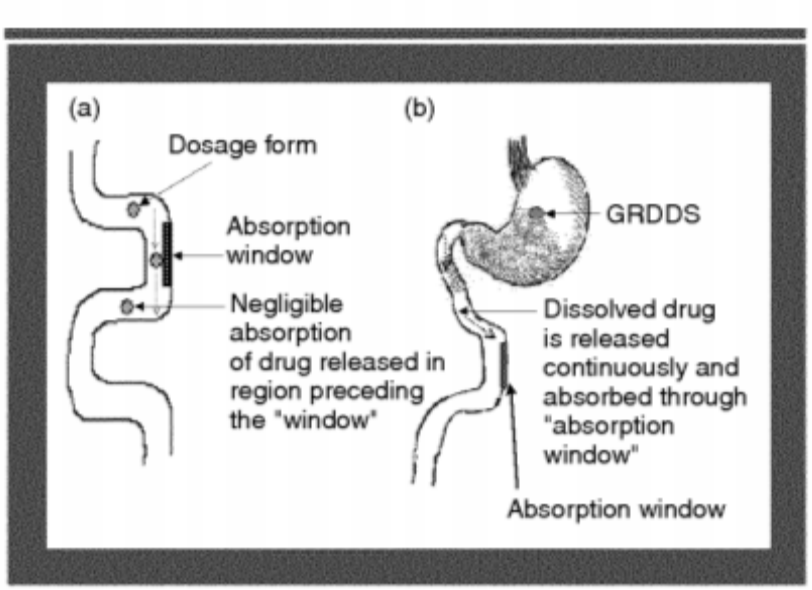

Figure 2: Drug absorption in the case of (a) conventional dosage forms and (b) gastroretentive drug delivery systems.

As mentioned under point 3.2 above, D1 gives the pharmacokinetic properties of pregabalin, namely a

rapid absorption with a C_{max} of 1.3 hours, a short half life of 4.6-6.8 hours, and a very high bioavailability of 90% (see Table on page 2813 and page 2815). This document does however not mention any "narrow absorption window" and does not give any evidence or hint that pregabalin is absorbed only in a certain region of the gastrointestinal tract, as shown by document D2. The pharmacokinetic parameters given in D1 show only that pregabalin has high dissolution and high permeability properties.

The EMEA Discussion D20 confirms the rapid absorption and high bioavailability disclosed in D1 (see page 7/42) and acknowledges that "pregabalin also is a substrate for the System L amino acid transporter of cell membranes that contribute to the permeation of pregabalin across membrane barriers" (see page 5/42). This is confirmed in D21 which states that "pregabalin is a substrate of the system L transporter, which is responsible for the transport of large amino acids across the brain and gut" (see page 16, left hand col. first par.). The same passage adds further that "pregabalin has been shown to rapidly penetrate the blood-brain barrier in the preclinical studies conducted in mice, rats, and monkeys". This document confirms also the rapid and extensive gastrointestinal absorption of pregabalin (see for instance "Summary"). D22 provides a more detailed analysis of the transport of pregabalin and demonstrates pregabalin to be a substrate for the Large Neutral Amino Acid (LNAA) carrier system in the rat ileum. D22 confirms that such studies can be extrapolated to humans by demonstrating that the absorption in the small intestine of the rat corresponds well with human oral absorption, and that there is a correlation between the in vitro/in situ rat intestinal permeability and fraction of drug absorbed

in humans. D19 explains that gastric retentive systems are useful for drugs with a restricted absorption window in the gastrointestinal tract (see paragraph linking pages 304 and 305). There is however no indication in this passage of D19 that pregabalin may be one of such drugs.

On reading these documents, it is evident that it was known that pregabalin has a rapid intestinal absorption and a high bioavailability and that it is absorbed through membranes, such as the gastrointestinal membrane or the blood barrier membrane, by an amino acid transporter system. None of the cited documents indicates however that pregabalin is absorbed through a "narrow absorption window" of the gastrointestinal tract, with a negligible absorption on regions preceding or following said window as shown in Figure 2 of D2.

Said documents do also not provide any evidence that the amino acid transporter system is localised only on a certain region of the gastrointestinal tract. The localisation of the amino acid transporter system on the terminal gastrointestinal portion, i.e. the ileal level, as shown in D22, or on the blood-barrier, as shown in D21, rather tends to show that this amino acid transporter system is widely widespread and does not appear to be localized in a "narrow absorption window" region of the gastrointestinal tract.

Consequently, the fact that pregabalin had a limited window of absorption in the gastrointestinal tract is not derivable from the cited prior art documents. It is however true that pregabalin is a highly soluble and highly permeable drug, and that there is indeed a need

for providing a dosage form adapted for a once a day administration.

3.6.3 It remains to determine whether the skilled person would make the choice of a GRDDS formulation based on the claimed excipients, for providing a composition suitable for once daily administration of pregabalin.

In order to provide a dosage form adapted for a once-a-day administration, the skilled person has a multitude of solutions at its disposal.

First of all, in the absence of any evidence of the existence of a "narrow window absorption" for pregabalin, the skilled person would have no reason to pursue a gastric-retained system. He would rather explore other options, such as simple conventional controlled-release formulations or sustained release forms containing a prodrug of pregabalin, as suggested in paragraph [0005] of the patent.

Moreover, even if a GRDDS were to be pursued, there is no clear incentive that would lead the skilled person to a size retention system as claimed. The skilled person would indeed have again the choice among many possible alternative solutions in the form of GRDDS, offering different mechanisms of action for the gastro-retention. This is for instance shown by document D2 which mentions the different possible gastro-retentive systems, such as floating systems, effervescent systems, bio-mucoadhesive systems, hydration-mediated systems, bonding-mediated adhesion, receptor mediated adhesion, swelling systems and high density systems (see pages 56-62). D3 also lists as possible gastro-retentive systems density based systems and adhesion-mucoadhesive systems. Similarly, D19 mentions several

mechanism of actions linked with gastro-retentive delivery systems, such as the addition of passage-delaying or high density agents, the modification of the size and shape of the delivery system, the use of bioadhesive systems or floating systems (see pages 304-305). The selection of a specific size retention system is therefore only a possibility among many alternative, for which there no is special incentive.

Finally, should the skilled person nevertheless consider that a GRDDS working by size retention is a suitable solution for solving the problem, there is also no hint to select the particular claimed excipients system, even if the combination of polyvinyl acetate and polyvinylpyrrolidone was known from documents D6, D7 or D8; D6 and D7 disclose indeed floating systems made from Kollidon® SR (PVAc and PVP) and D8 discloses a sustained release dosage form made from the same Kollidon® SR. There is however no motivation for the skilled person to further modify the compositions shown in D6-D8 in any way, let alone by inclusion of a specific disintegrating agent, namely cross-linked polyvinylpyrrolidone. As already reported in paragraphs 3.2 and 3.6 of the decision under appeal, the data presented in the application and in D13 show that the claimed tablets function as swelling and floating controlled release dosage forms, and that they maintain these properties even when compressed with a force that is high enough to provide hard tablets. In particular, D13 shows that the substitution of high-molecular weight PVP for cross-linked PVP causes the loss of the useful characteristics of the claimed tablets when so compressed.

The skilled person therefore faces multiple choices at different levels and, in the absence of any particular

incentive or technical evidence, the provision of a composition as claimed cannot be considered to be obvious.

3.7 Consequently, the subject-matter of claim 1 is inventive and the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated