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Datasheet for the decision of 23 November 2021

Case Number: T 0171/19 - 3.3.01

Application Number: 12712189.5

Publication Number: 2685979

IPC: A61P25/00, A61P25/24, A61P25/18

Language of the proceedings: EN

Title of invention:
INJECTABLE PHARMACEUTICAL COMPOSITIONS COMPRISING A WATER-INSOLUBLE ANTI-PSYCHOTIC, SORBITAN LAURATE AND POLYSORBATE 20

Patent Proprietor:
Alkermes Pharma Ireland Limited

Opponent:
Generics (UK) Ltd

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

Keyword:
Inventive step - (yes)

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Case Number: T 0171/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 23 November 2021

Appellant: (Patent Proprietor)	Alkermes Pharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 (IE)
Representative:	Harris, Jennifer Lucy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Appellant: (Opponent)	Generics (UK) Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 7 December 2018 concerning maintenance of the European Patent No. 2685979 in amended form.**

Composition of the Board:

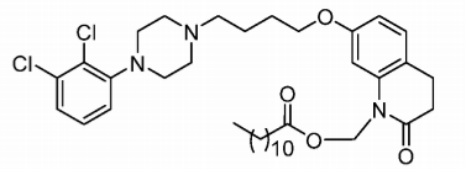
Chairman	A. Lindner
Members:	R. Hauss
	P. de Heij

Summary of Facts and Submissions

I. European patent No. 2 685 979 (patent in suit) was granted with a set of 23 claims. The independent claims read as follows:

1. A pharmaceutical composition comprising:

(a) compound A-7



A-7

(b) sorbitan laurate;

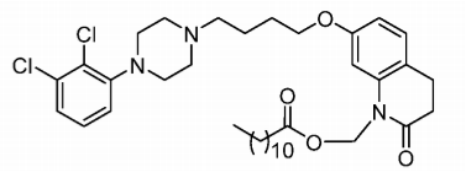
(c) polysorbate 20; and

(d) an aqueous vehicle;

wherein the composition forms an aqueous, flocculated, injectable suspension.

13. An injectable pharmaceutical composition comprising:

(a) compound A-7:



A-7

wherein component (a) is in a weight ratio of approximately 15 - 35%;

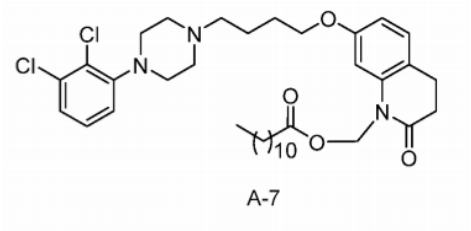
(b) sorbitan laurate in a weight ratio of approximately 0.2 - 1%

(c) polysorbate 20 in a weight ratio of approximately 0.05 - 0.8%; and

(d) an aqueous carrier.

14. *An injectable composition comprising:*

(a) compound A-7:



A-7

(b) sorbitan laurate;

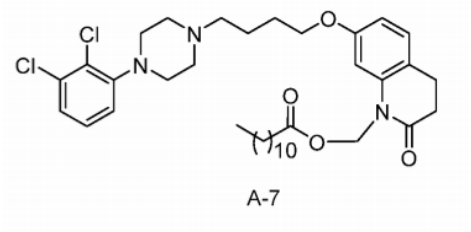
(c) polysorbate 20; and

(d) an aqueous vehicle.

17. *The composition of any one of claims 1 to 16 for use in a method for treating disorders of the central nervous system.*

20. *A pharmaceutical composition comprising:*

(a) 24 - 30 weight percent compound A-7:



A-7

(b) 0.2 - 1 weight percent sorbitan laurate;

(c) 0.1 - 0.3 weight percent polysorbate 20; and

(d) an aqueous vehicle.

II. Another name for compound A-7 mentioned in the claims is **aripiprazole lauroxil**.

III. Notice of opposition was filed, opposing the patent in suit under Article 100(a), (b) and (c) EPC on the following grounds: The claimed subject-matter did not involve an inventive step; it was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art; and it

extended beyond the content of the application as filed.

IV. The patent proprietor requested that the opposition be rejected (main request) and filed a number of auxiliary requests.

V. The documents cited in the proceedings before the opposition division included the following:

D1: US 2009/0163519 A1

D2: WO 2010/151711 A1

D6: Handbook of Pharmaceutical Excipients: "Sorbitan Esters" (undated)

D19: R.C. Rowe et al.: Handbook of Pharmaceutical Excipients, 6th ed. (2009), 675-678, "Sorbitan Esters"

VI. The decision under appeal is the opposition division's interlocutory decision, announced on 16 November 2018 and posted on 7 December 2018, finding that the patent as amended in the form of the first auxiliary request met the requirements of the EPC.

With regard to the main request, the opposition division held that the grounds of opposition under Article 100(b) and (c) EPC did not prejudice maintenance of the patent as granted. However, the subject-matter of the claims as granted did not involve an inventive step (Article 100(a) EPC):

Document D2 (specifically page 46: compound 7 and Example 68, Table J on pages 187-189) was the closest prior art. The composition according to independent claim 14 as granted differed from that disclosed in D2 (page 189, first line of Table J) through the presence of sorbitan laurate. The objective technical problem was to provide an alternative composition for the

administration of aripiprazole lauroxil. Considering the disclosure of surface modifiers and wetting agents in supplementary document D1, it would have been obvious for the person skilled in the art to combine polysorbate 20 with sorbitan laurate, thus getting to the subject-matter of claim 14. The subject-matter of independent claims 1, 13 and 20 as granted did not involve an inventive step either.

VII. Both the opponent and the patent proprietor appealed against the opposition division's decision.

VIII. In point 3.10 of its statement setting out the grounds of appeal, the patent proprietor included a table presenting new experimental data.

IX. Oral proceedings were held on 23 November 2021 in the absence of the opponent. The latter had withdrawn its request for oral proceedings and advised the board that it would not be attending (Article 15(3) RPBA and Rule 115(2) EPC).

X. The patent proprietor's arguments, as far as relevant to the present decision, may be summarised as follows:

Inventive step - main request

Starting from the disclosure of document D2, the technical problem was to provide an improved suspension composition of aripiprazole lauroxil which could be more easily manufactured. Reference was made to entries 4 and 12 in Table 1 of the patent in suit. These showed by comparison that adding sorbitan laurate to the suspension medium resulted in improved wetting characteristics, owing to an increase in the value of the spreading coefficient. This meant that less energy would be needed to prepare the suspension.

The supplementary data provided in point 3.10 of the patent proprietor's grounds of appeal showed that an increase in the value of the spreading coefficient had been observed for all compositions containing sorbitan laurate, irrespective of the ratio of sorbitan laurate to polysorbate 20.

The prior art did not provide any pointer to combine the surfactants sorbitan laurate and polysorbate 20 in order to achieve improved wetting or facilitate suspension compounding.

Admittance of evidence

The new data presented with the patent proprietor's grounds of appeal was highly relevant. The data had been supplied in response to an issue put forward for the first time at the oral proceedings before the opposition division and in the decision under appeal.

XI. The opponent no longer pursued the objections under Article 100(b) and (c) EPC in its appeal submissions.

The opponent's arguments (presented in writing), as far as relevant to the present decision, may be summarised as follows:

Inventive step - main request

Starting from the description in document D2 of a suspension containing aripiprazole lauroxil, the objective technical problem was to provide an alternative composition.

Contrary to the patent proprietor's view, there was no evidence of a technical effect across the scope claimed that could provide a basis for defining the technical problem as the provision of an improved formulation. In particular, there was no evidence of the alleged

advantage of easier processing, attributed in the patent in suit to a numerically positive spreading coefficient.

Adding sorbitan laurate to provide an alternative composition would have been an obvious measure. Indeed, D2 itself suggested the use of fatty acid esters of sorbitan (D2: page 159, line 29), and sorbitan laurate was a commonly known fatty acid ester. Documents D1 (paragraph [0034]) and D6 illustrated the skilled person's awareness of sorbitan laurate.

This assessment concerned claim 14 as granted, but it applied equally to the other independent claims.

Admittance of evidence

The experimental data presented for the first time with the patent proprietor's grounds of appeal was irrelevant, since it could not be considered conclusive evidence of easier processing or of an effect obtained across all ratios of sorbitan laurate to polysorbate 20.

XII. The appellant-opponent requested in writing that the decision under appeal be set aside and that the patent in suit be revoked.

Within the purview of this request, the opponent also requested that the new data regarding wettability filed by the patent proprietor in point 3.10 of its grounds of appeal be not admitted into the proceedings under Article 12(4) RPBA 2007.

XIII. The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted;

or, in the alternative, that the opponent's appeal be dismissed and the patent be maintained in the form of the first auxiliary request of 14 September 2018 as held allowable in the decision under appeal;

or, in the further alternative, that the patent be maintained on the basis of the claims of one of: auxiliary requests 2 to 11 (as filed on 14 September 2018), auxiliary request 12 (as filed on 17 November 2017) or auxiliary requests 13 and 14 (as filed on 14 September 2018).

Reasons for the Decision

1. Admissibility of the appeals

The appeals comply with Articles 106 to 108 EPC and Rule 99 EPC; they are admissible.

2. Inventive step - main request (Articles 100(a), 52(1) and 56 EPC)

Patent in suit

2.1 The patent in suit seeks to provide injectable pharmaceutical compositions that are useful for delivering water-insoluble anti-psychotic drugs and prodrugs for extended-release use, in particular aripiprazole lauroxil (see paragraphs [0001], [0008], [0025], [0026] of the patent specification).

2.2 The claims as granted include four independent product claims, namely claims 1, 13, 14 and 20 (see point I above). Furthermore, independent claim 17 relates to a medical use of the compositions of claims 1 to 16.

2.2.1 The product claims define a (pharmaceutical) composition comprising:

(a) compound A-7 (aripiprazole lauroxil),
(b) sorbitan laurate,
(c) polysorbate 20 and
(d) an aqueous vehicle (claims 1, 14, 20) or carrier (claim 13).

2.2.2 By the nature of their components, the claimed compositions are suspensions. Claims 1, 13 and 14 require the composition to be injectable. Claims 13 and 20 specify concentration ranges for components (a) to (c).

Starting point in the prior art

2.3 Document D2 relates to prodrugs designed for sustained drug delivery. One of the prodrugs according to D2 is aripiprazole lauroxil (see D2: page 46, compound 7).

On page 189 (first line of Table J), D2 discloses an injectable (see page 187, lines 19 ff.) suspension composition comprising (a) aripiprazole lauroxil (compound 7 in D2), suspended in (d) a phosphate-buffered saline vehicle ("PBS"). The composition also contains hydroxypropyl methyl cellulose ("HPMC") and (c) polysorbate 20 ("Tween 20").

2.4 It was common ground that this composition in D2 was the closest prior art and that the composition according to claim 14 as granted differed from it by further including (b) sorbitan laurate.

Objective technical problem and solution

2.5 The patent in suit reports in Example I (see paragraphs [0082] and [0083]) that the formulation development for aripiprazole lauroxil focused on improving the wettability and redispersibility

characteristics of the injection vehicle. The aim was thereby to improve the physical properties of the drug suspension, namely ease of manufacturing and resuspendability. A wide array of injection vehicles were screened to identify promising candidates for further optimisation.

2.6 The first round of experiments assessed wettability characteristics of various vehicles with aripiprazole lauroxil, namely the parameters "free energy of immersion" and "spreading coefficient".

2.7 The injection vehicles to be tested were made by dissolving the appropriate mass of excipients in a metered volume of water for injection (see the patent in suit, paragraph [0084]).

2.8 The methodology used for determining the parameters is described in Example I (paragraphs [0086] ff.). Results are reported in Table 1 (see paragraph [0093]).

2.9 Entries 4 and 12 of Table 1 are compared as follows:

Entry	***Vehicle Formulation [% w/v] in water***	***Free Energy of Immersion [mN/m]***	***Spreading Coefficient [mN/m]***
4	4% PEG3350 0.5% polysorbate 20 0.8% sorbitan laurate	-29	2.6
12	4% PEG3350 0.5% polysorbate 20	-27	-6.5

2.10 Entry 4 represents a vehicle formulation in conformity with claim 14, with components (b), (c) and (d). Entry 12 represents a vehicle formulation as described in document D2, with components (c) and (d).

The sole difference between the two formulations is the presence of sorbitan laurate (feature (b)) in the vehicle formulation of entry 4.

2.11 The free energy of immersion of the formulations was in the same range, considered to be thermodynamically favourable (see paragraph [0094] of the patent in suit).

2.12 In support of its reasoning in favour of an inventive step, the patent proprietor relied solely on the difference in the spreading coefficients of the formulations. The alleged advantage was that suspensions as defined in claim 14 containing sorbitan laurate could be prepared more easily.

In this context, the patent in suit explains that a positive spreading coefficient means that wetting, i.e. the replacement of the air-solid interface by the liquid-solid interface, will occur spontaneously, i.e. without the addition of work. This is desirable because of an increased likelihood of complete deaggregation/wetting of the powder during suspension compounding, leading to an overall ease of processing (paragraph [0095]).

2.13 The opponent did not contest the parameter values reported in the patent. It argued, however, that it had not been shown that the observed difference in the numeric values of the spreading coefficients actually had an impact on the ease of processing.

2.14 This argument does not succeed. Since the required energy input will be lower when spontaneous wetting occurs, it is technically plausible that suspension preparation could be facilitated in such a case.

In these circumstances, the onus would have been on the opponent to provide evidence to the contrary (e.g. that the alleged effect would not occur, or would be negligible, for all or some embodiments encompassed by the claim).

2.15 Hence, the objective technical problem is to provide a suspension formulation of aripiprazole lauroxil that allows easier manufacturing.

2.16 In the absence of evidence to the contrary, the board accepts that the compositions according to claim 14 solve this technical problem.

New data filed by the patent proprietor

2.17 In the decision under appeal, the opposition division had reasoned that there was a correlation between the properties (i) redispersibility of the settled suspensions and (ii) wettability. Based on resuspension times reported in Table 4 of the patent, the opposition division had concluded that a minimum ratio of sorbitan laurate to polysorbate 20, which must be above 0.5:0.8, was required to obtain an improvement in either property. Since the claims as granted did not define such a minimum ratio, the opposition division had taken the view that the alleged technical effects, including improved wettability, had not been credibly established across the scope claimed (see the decision under appeal, point 13.4.2 on page 14). The opposition division thus defined the objective technical problem as the provision of an alternative composition.

2.18 In order to counter this reasoning contained in the decision under appeal, the patent proprietor filed new data regarding wettability in point 3.10 of its grounds of appeal. The new data consisted of spreading

coefficient values of compositions containing varying ratios of sorbitan laurate and polysorbate 20.

2.19 The board decided to admit the patent proprietor's new data into the proceedings as the data had been filed in response to a line of argument regarding the alleged effect of improved wettability (see point 2.17 above) which appears in the written file for the first time in the decision under appeal (Article 12(4) RPBA 2007).

2.20 The new data had been obtained with compositions containing phosphate-buffered saline (0.8% NaCl) and polysorbate 20 ("PS20") either alone or in combination with sorbitan laurate ("SML") in varying ratios.

Formulation	Spreading Coefficient (mN/m)
1.0% PS20	-20.17
0.8% PS20 0.5% SML	-5.24
1.0% PS20 0.5% SML	-3.02
0.5% PS20 1.0% SML	0.48

2.21 In this context, the opponent pointed out that only one composition had the positive spreading coefficient associated in the patent with "easier processing". This meant that the opposition division had been correct to conclude that, even if this effect were relevant, wettability was also dependent on the ratio of the surfactants, not just on the presence of sorbitan laurate.

2.22 The patent proprietor argued that the results showed the most negative spreading coefficient value for the composition containing only polysorbate 20 but not sorbitan laurate. Irrespective of the surfactant ratio, all compositions containing sorbitan laurate had increased spreading coefficient values in comparison. Whilst a positive spreading coefficient was optimal in that it indicated that spreading would occur

spontaneously, a less negative spreading coefficient still indicated that less work would be required to form a wetted suspension in comparison with a more negative spreading coefficient. Such energy input might be, for example, the application of high shear and/or high temperature. Any reduction in the requirement for such energy input was desirable for manufacturing pharmaceutical compositions.

2.23 The board considers that the patent proprietor's argument is technically plausible and in line with its previous submissions. The opponent did not support its own argument (i.e. that no appreciable effect would be achieved) with evidence.

2.24 Wettability is a measure of the energy input required to initially form a wetted suspension, whereas redispersibility is the ability of a suspension that has been formed, and subsequently allowed to settle, to resuspend.

2.25 As set out in the patent proprietor's grounds of appeal, wettability is not directly correlated with redispersibility, although it may influence this property (statement setting out the grounds of appeal, point 3.8). The opponent did not dispute the patent proprietor's assertion in this regard.

2.26 In any case, when considering spreading coefficients and their technical effect on the initial preparation of the suspensions, there is no reason to assume that a requirement for a specific minimum ratio of sorbitan laurate to polysorbate 20 could be inferred from Table 4 of the patent in suit. Table 4 reports values for a different parameter (namely resuspension time).

2.27 In conclusion, the new data and the opponent's speculative arguments about surfactant ratios do not change the board's assessment regarding the alleged technical effect and the formulation of the objective technical problem (see points 2.14 to 2.16 above).

Obviousness of the solution

2.28 Neither D2 nor the other prior-art documents cited by the opponent suggest that the formulation according to claim 14 solves the objective technical problem to provide a suspension formulation of aripiprazole lauroxil that allows easier manufacturing. In fact, the opponent did not argue that the claimed formulation would have been an obvious solution to this specific technical problem.

2.28.1 D2 mentions fatty acid esters of sorbitan as possible components of liquid oral dosage forms (page 159, line 29), but does not suggest combining sorbitan laurate with polysorbate 20. Sorbitan laurate (also known as sorbitan monolaurate or Span 20) is known as a pharmaceutically acceptable surfactant and wetting agent. It is mentioned in documents D1 and D19 as a possible component of injectable suspension formulations for intramuscular administration (D1: claims and paragraphs [0001] and [0034]; D19: Table IV and last sentence of point 7). Neither document relates to aripiprazole lauroxil.

2.28.2 Although it is common to use blends of surfactants, there is no specific teaching in these documents that adding sorbitan laurate to an aqueous suspension vehicle containing polysorbate 20 might facilitate the preparation of a suspension of aripiprazole lauroxil in the vehicle.

2.28.3 (As an explanatory remark, D6 cited by the opponent in this context (see point XI. above) is a copy from the "Handbook of Pharmaceutical Excipients", which was filed without evidence of its publication date (see also point 6 of the opposition division's communication of 16 March 2018). The opponent later filed D19, which has largely the same content, as a "more up to date version of D6" (see paragraph (18) in the opponent's letter of 14 September 2018). The board has referred in its remarks to D19, which has an identifiable publication date, rather than D6. This does not make a difference for the purposes of this discussion.)

2.29 For these reasons, the subject-matter of claim 14 as granted involves an inventive step within the meaning of Article 56 EPC.

2.30 The same reasoning and conclusion apply to the other independent claims as well as to the dependent claims.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated