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Datasheet for the decision of 8 September 2023

Case Number: T 1161/22 - 3.3.07

Application Number: 19150745.8

Publication Number: 3492080

IPC: A61K31/4468, A61K31/5517, A61P25/20, A61P25/04, A61K9/00

Language of the proceedings: EN

Title of invention:
DOSING REGIMEN FOR SEDATION WITH CNS 7056 (REMIMAZOLAM)

Applicant:
PAION UK Ltd.

Headword:
DOSING REGIMEN FOR SEDATION WITH CNS 7056 (REMIMAZOLAM)/Paion UK Ltd

Relevant legal provisions:
EPC Art. 76(1)
RPBA 2020 Art. 13(2)

Keyword:
Divisional application - added subject-matter (yes)
Request filed during oral proceedings - Admissible (Yes)

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Case Number: T 1161/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 8 September 2023

Appellant: (Applicant)	PAION UK Ltd. Chivers Way Histon Cambridge CB24 9ZR (GB)
Representative:	König Szynka Tilmann von Renesse Patentanwälte Partnerschaft mbB Düsseldorf Mönchenwerther Straße 11 40545 Düsseldorf (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 30 November 2021 refusing European patent application No. 19150745.8 pursuant to Article 97(2) EPC.**

Composition of the Board:

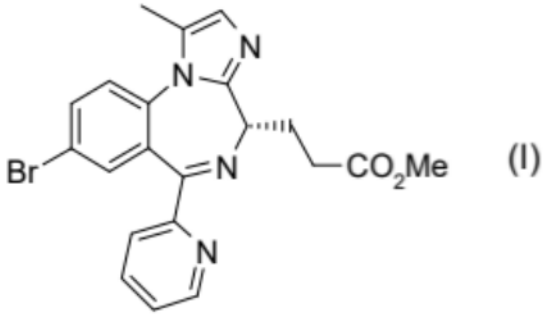
Chairman	A. Usuelli
Members:	D. Boulois
	L. Basterreix

Summary of Facts and Submissions

I. The appeal lies from the decision of the examining division to refuse European patent application n° 19150745.8, which was a divisional application of EP 11794020.5 published as WO 2012/062439 . The decision was based on 12 sets of claims filed with letter of 2 November 2020 as main request and auxiliary requests 1-11 filed with letter of 17 September 2021.

Claim 1 of the main request read:

"1. 3-[(4S)-8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo[1,2-a][1,4]benzodiazepine-4-yl]- propionic acid methyl ester (CNS 7056) of formula (I)



(I)

or a pharmaceutically acceptable salt or solvate thereof for use in sedation, wherein CNS 7056 is given in a fixed dose, wherein the term “fixed dose” relates to an amount of a drug given to a patient irrespective of his body weight and the fixed dose is between 5 and 9 mg."

II. According to the decision under appeal, none of the requests met the requirements of Article 76(1) EPC in view of the claimed combination of the features

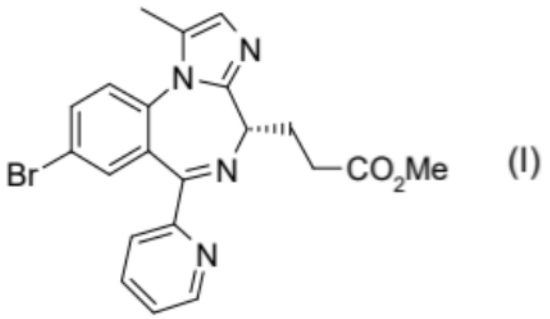
III. The patent applicant (hereinafter the appellant) filed an appeal against the first instance decision.

IV. With its statement of grounds of appeal dated 11 April 2022, the appellant maintained the main request and auxiliary requests 1-11 that were filed during the examination proceedings.

V. A communication expressing the Board's preliminary opinion was issued on 20 April 2023. The Board's opinion was that none of the requests met the requirements of Article 76(1) EPC.

VI. Oral proceedings before the Board of appeal took place on 8 September 2023. During the oral proceedings, the appellant withdrew auxiliary requests 1-11 and filed a new auxiliary request 12. Claim 1 of auxiliary request 12 read as follows, with the modifications vis-à-vis the main request shown in bold:

"1. 3-[(4S)-8-bromo-1-methyl-6-(2-pyridinyl)-4H-imidazo[1,2-a][1,4]benzodiazepine-4-yl]- propionic acid methyl ester (CNS 7056) of formula (I)



(I)

or a pharmaceutically acceptable salt or solvate thereof for use in sedation **for colonoscopy**, wherein CNS 7056 is given **by intravenous administration** in a fixed dose, wherein the term “fixed dose” relates to an

amount of a drug given to a patient irrespective of his body weight, **the fixed dose is 5 mg, 6 mg, 8 mg, or 9 mg and at least one 3 mg top-up dose of CNS 7056 is given."**

VII. The appellant's arguments can be summarised as follows:

Main request - Article 76(1) EPC

The basis for claim 1 of the main request could be found in the studies CNS 7056-1 and CNS 7056-2 in the parent application, in particular in the simulated data of example 1 in Table 18 of page 27. The table on page 5 indicated the assessment of alertness and sedation scale, i.e the Modified Observer's Assessment of Alertness/Sedation scale (MOAA/S) which was used in Table 18, and which went from the score 0 (Does not respond to deep stimulus) to the score 6 (agitated). Page 20, lines 8-20 gave further information on this MOAA/S scale.

Table 18 showed that 21% of the subjects were in sedation after the first dose, which constituted the basis for the medical indication.

Figure 6 of the parent application was the basis for the claimed dose range of "between 5 and 9 mg".

Admission of auxiliary request 12 into the appeal proceedings

The request was admissible in view of exceptional circumstances. The appellant was given by the Board for the first time during oral proceedings the reasons why claim 1 of the main request did not meet the

requirements of Article 76(1) EPC, in particular with regard to some missing features. The modifications made to claim 1 overcame the objections and were admissible also for this reason. Moreover, the appeal did not concern the dependent claims, which were objected for the first time by the Board in its communication, which justified their suppression in this request

Auxiliary request 12 - Article 76(1) EPC

Features regarding the way of administration, the subject, the top up doses were incorporated in claim 1. The dependent claims were deleted. The same basis as for the main request could be found in Table 18 and the general context of example 1. The feature "at least one 3 mg top-up dose of CNS 7056 is given" could be found in the first column of Table 18. The top up dose was always given as seen in the average number of top up doses given in the last column of Table 18.

VIII. Requests

The appellant requested that the decision under appeal be set aside and that the application be remitted to the examining division for further prosecution on the basis of the set of claims filed as main request with letter of 2 November 2020 or on the basis of auxiliary request 12 filed during the oral proceedings of 8 September 2023.

Reasons for the Decision

1. Main Request - Article 76(1) EPC

1.1 The subject-matter of claim 1 of the main request relates essentially to the compound CNS 7056 for use in sedation, wherein CNS 7056 is given in a fixed dose between 5 and 9 mg.

1.2 According to the appellant, a basis for claim 1 can be found in particular in Example 1, Table 18 and Figure 6 of the parent application (see WO 2012/062439), in particular in specific columns of Table 18. The Board agrees that these are the most relevant parts of the parent application, since the general disclosure of said parent application relates to the combination of CNS 7056 with an opioid, in particular fentanyl, for the use in sedation. Hence, only the cited specific parts of the parent application may serve as a basis for the subject-matter of claim 1.

1.3 On page 12, first paragraph, the application mentions two studies used in example 1, i.e CNS-7056-001 and CNS 7056-003 in which CNS 7056 was administered as a single agent in a context of a comparison with a concomitant administration of fentanyl in study CNS 7056-002.

In Example 1, details on the study CNS 7056-001 are further given. The relevant passage (page 14 line 40 to page 15, line 3) reads: "Pharmacokinetic data were obtained after CNS 7056 had been administered by intravenous infusion over one minute to groups of healthy volunteers at the following doses: 0.01 , 0.025, 0.05, 0.075, 0.1 , 0.15, 0.2, 0.25 and 0.3 mg/ kg. Both arterial (1 , 2, 3, 4, 6, 8, 10, 12, 15, 20, 30, 45 minutes and 1 , 2, 3, 4 hours post-dose) and

venous (2, 3, 4, 6, 8, 12 hours) blood samples containing CNS 7056 and its metabolite, CNS 7054, were obtained from indwelling catheters. Concentrations of CNS 7056 and CNS 7054 were measured using HPLC with tandem mass spectrometric detection. Measurements of sedation (MOAA/S and Bispectral Index (BIS) scores) and systolic and diastolic blood pressure were made at regular intervals."

Table 18 reports the results of a simulation of various dosing regimens. The simulation is based on CNS 7056 and fentanyl interaction performed in example 1. The Table mentions several combinations of loading doses and top-up doses of CNS 7056 in combination with different fentanyl doses, including a dose of 0 µg of fentanyl, i.e CNS 7056 alone; it shows that CNS 7056 alone provides a sedation, as shown by the results of the column "Zero MOAA/S Scores", i.e the highest score for sedation (see table on page 5). The doses of CNS 7056 are comprised between 5 and 9 mg and are followed by top-up doses of 3 mg when CNS 7056 is given alone. Table 18 is as follows:

Table 18

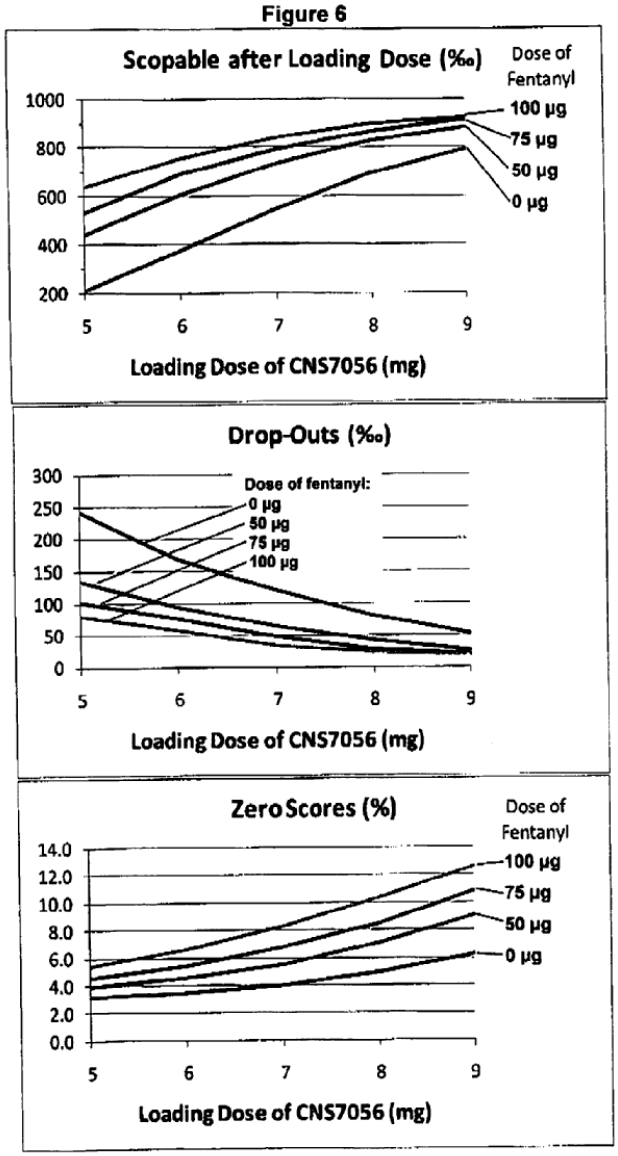
CNS 7056 Regimen[a] (mg)	Fentanyl Dose (µg)	CNS 7056-Fentanyl Gap (min)	Dropouts (‰)	Zero MOAA/S Scores (%)	Failures (‰)	Scoped after Loading Dose (‰)	Average no. of Top-ups
6/4[a]	50	4 min	42	9.95	86	604	3.955
6/4	75	4 min	28	10.6	87	689	3.899
6/4	100	4 min	24	11.8	83	754	3.806
5/3	0	4 min	242	3.17	116	211	4.205
5/3	50	4 min	133	3.88	168	437	4.412
5/3	75	4 min	102	4.53	175	529	4.423
5/3	100	4 min	79	5.39	174	637	4.394
6/3	0	4 min	168	3.42	148	374	4.337
6/3	50	4 min	93	4.51	197	604	4.387
6/3	75	4 min	75	5.39	194	689	4.335
6/3	100	4 min	57	6.60	194	754	4.292
7/3	0	4 min	119	4.00	161	545	4.338
7/3	50	4 min	64	5.51	170	735	4.31
7/3	75	4 min	47	6.83	166	791	4.259
7/3	100	4 min	33	8.30	166	839	4.211
8/3	0	4 min	80	4.91	159	694	4.295
8/3	50	4 min	42	7.08	156	829	4.208
8/3	75	4 min	27	8.47	162	868	4.151
8/3	100	4 min	24	10.3	143	897	4.072
9/3	0	4 min	52	6.20	153	793	4.219
9/3	50	4 min	26	9.02	147	882	4.087
9/3	75	4 min	20	10.8	138	913	4.017
9/3	100	4 min	18	12.6	130	925	3.925

a Loading dose / Top-up doses

Table 18 is mentioned in the description on page 21, and said passage relates to the simulations based on the CNS 7056-fentanyl interaction. The description on pages 20 and 21 gives further details on the studies made. In particular it is explained that the studies are made in the context of assessing the efficacy of the drugs in patients undergoing a colonoscopy (see for instance page 20, line 38 or page 21, line9).

Figure 6 is related to the experiments of Table 18 and comprises three graphic representations of respectively "Scopable after loading dose", "Drop-outs" and "Zero Scores" expressed in units per thousand, according to several doses of fentanyl, which might be 0 µg. Figure 6 is as follows:

Figure 6



1.4 In the Board's view, the subject-matter of claim 1 of the main request appears to have been selected from different parts of the description, in particular from Table 18 and Figure 6, out of the context in which they were disclosed, and generalised.

Table 18 is based on two experimental studies characterised by a specific protocol of administration, i.e by intravenous administration and by specific doses followed by specific top-up doses, which are not expressed in claim 1 of the main request. Moreover, as

explained above, the assessment of the sedation is made in the context of a colonoscopy.

Moreover, the parts of the parent application referred to by the appellant disclose specific or fixed doses of CNS 7056 comprised between 5 and 9 mg, but they do not disclose the range of a fixed dose "between 5 and 9 mg"; this range is neither found in Table 18, nor in its corresponding Figure 6, which relate all to the same specific fixed doses of 5, 6, 7, 8 and 9 mg. Ranges of fixed doses of CNS 7056 are disclosed for instance in claim 1 and on page 8 (lines 20-27); however, they clearly refer to treatments that also involve the administration of an opioid and cannot be combined with the claimed subject-matter of claim 1.

In view of the above, the Board concurs with the decision of the examining division that the subject-matter of claim 1 is not derivable directly and unambiguously from the parent application.

1.5 Hence, the subject-matter of claim 1 of main request does not comply with the requirements of Article 76(1) EPC.

2. Auxiliary request 12 - Admission into the proceedings

2.1 This request has been filed during the oral proceedings before the Board and comprises an unique claim 1 which has been amended by several features. According to the appellant, the modifications correspond to points raised for the first time by the Board during oral proceedings for the assessment of Article 76(1) EPC.

2.2 According to Article 13(2) RPCR 2020, amendments to a party's case made after notification of a summons to

oral proceedings are not taken into account, except in exceptional circumstances.

Auxiliary request 12 was filed during oral proceedings. In its communication, the Board issued for the first time objections under Article 76(1) EPC against the dependent claims of the main request. Moreover, during oral proceedings, the Board provided specific explanations with regard to the objections under Article 76(1) EPC raised against claim 1 of the main request. The Board notes that the amendments made to claim 1 correspond to the points raised during oral proceedings.

In the present case, the Board accepts that there are exceptional circumstances justifying its admission into the proceedings, as this request might constitutes an appropriate response to an objection under Article 76(1) EPC first raised in the notification under Article 15(1) RPCR 2020 or explained precisely during oral proceedings.

Consequently, the Board decides to admit auxiliary request 12 into the appeal proceedings (Article 13(2) RPBA 2020).

3. Auxiliary request 12 - Article 76(1) EPC

Claim 1 of auxiliary request 12 has been amended by the features "for colonoscopy", "by intravenous administration" and "the fixed dose is 5 mg, 6 mg, 8 mg, or 9 mg" and "at least one 3 mg top-up dose of CNS 7056 is given".

With regard to the top-up doses, the Board notes that Table 18 discloses, when 0 µg of fentanyl is given, a

constant top-up dose of 3 mg of CNS 7056 and an average number of top-up doses comprised between 4.205 and 4.338 (cf. the right hand column of Table 18), but does not give the actual number of top-up doses given. Hence, there is no disclosure of "at least one 3 mg top-up dose of CNS 7056" in the Table and this feature is also not derivable therefrom. For instance, there is no disclosure in Table 18 of one or two top-up doses.

The Board could in particular not agree with the appellant that dependent claim 2 of the parent application could serve as a basis for this feature; said claim recites indeed that "at least one top-up dose of CNS 7056 is given". Claim 2 is however dependent on claim 1 which relates to the combination of CNS 7056 with an opioid, which is not the subject-matter of claim 1 of auxiliary request 12.

Consequently, the subject-matter of claim 1 of auxiliary request 12 is not derivable directly and unambiguously from the parent application and auxiliary request 12 does not meet the requirements of Article 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sanchez Chiquero A. Usuelli

Decision electronically authenticated