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Datasheet for the decision of 14 December 2020

Case Number: T 0978/18 - 3.3.01

Application Number: 10011789.4

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Title of invention:
Tamper-resistant oral opioid agonist formulations

Patent Proprietor:
EURO-CELTIQUE S.A.

Opponent:
Krka, d.d., Novo mesto

Relevant legal provisions:
EPC Art. 76(1), 83, 54, 56

Keyword:
Divisional application - added subject-matter (yes) - main requests and auxiliary requests I to IV
Sufficiency of disclosure - (yes)
Novelty - (yes)
Inventive step - (yes)

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Case Number: T 0978/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 14 December 2020

Appellant: (Opponent)	Krka, d.d., Novo mesto Smarjeska cesta 6 8000 Novo mesto (SI)
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Representative:	Maiwald Patent- und Rechtsanwaltsgesellschaft mbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 14 March 2018 concerning maintenance of the European Patent No. 2277521 in amended form.**

Composition of the Board:

Chairwoman	M. Pregetter
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 2277521 (patent in suit) derives from European patent application No. 10011789.4, which is a divisional of European patent applications No. 01909086.9 (published as WO 01/58451 A1) and 09006024.5 (published as EP 2092936 A2, in turn a divisional of application No. 01909086.9).

II. The patent in suit was granted with a set of 13 claims. The independent claims read as follows:

"***1.*** *An oral dosage form comprising*

(i) an opioid agonist and

(ii) an opioid antagonist composition comprising an opioid antagonist dispersed in a matrix that renders the antagonist substantially non-releasable when the dosage form is administered orally intact, wherein the matrix comprises one or more of a pharmaceutically acceptable hydrophobic material and the antagonist is unavailable to be absorbed during its transit through the gastrointestinal system.

12. *The opioid antagonist composition of claim 1, wherein the matrix is in the form of pellets.*

13. *The opioid antagonist composition of claim 1, wherein the opioid antagonist composition is in the form of a granulation comprising the opioid antagonist and the hydrophobic material(s).*"

III. The patent in suit was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was

not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

IV. In the proceedings before the opposition division, the patent proprietor requested that the opposition be rejected (main request) and submitted six sets of claims as auxiliary requests I to VI. The independent claims in all auxiliary requests were identical to the independent claims as granted.

V. The documents cited in the course of the opposition and appeal proceedings included the following:

D1: WO 99/32120 A1

D2: WO 99/32119 A1

D3: WO 97/33566 A2

D14: G. S. Banker, C. T. Rhodes (editors): Modern Pharmaceutics, 3rd ed., Chapter 15, pages 575 to 593, Marcel Dekker, New York (1995)

VI. The decision under appeal is the opposition division's interlocutory decision, announced on 19 October 2017 and posted on 14 March 2018, rejecting the patent proprietor's main request and finding that the patent as amended in the form of auxiliary request I met the requirements of the EPC.

VII. According to the decision under appeal:

(a) The claims as granted (main request), specifically dependent claim 11, did not meet the requirements of Article 76(1) EPC.

(b) The claims of auxiliary request I complied with Articles 76(1) and 123(2) EPC.

(c) On the basis of common general knowledge and the guidance given in the patent in suit, the person skilled in the art was able to prepare dosage forms as defined in the claims (Article 83 EPC).

(d) Owing to differences in the structure of the dosage forms and the release characteristics, the subject-matter claimed in auxiliary request I was novel over the disclosure of documents D1 and D2.

(e) The claimed subject-matter also involved an inventive step: starting from the technical teaching of document D3, the objective technical problem was to provide an alternative oral dosage form comprising an opioid agonist and an opioid antagonist, suitable for providing effective analgesia while exhibiting a reduced abuse potential. The solution to that problem consisted in employing a matrix comprising a hydrophobic material to render the antagonist substantially non-releasable. This solution was not obvious since the person skilled in the art would not have departed from the basic general concept of document D3, which focused on a different type of dosage form, namely an osmotic push-pull system. Documents D1 or D2, or common general knowledge as represented by document D14, did not render the claimed subject-matter obvious either.

VIII. The opponent (appellant) appealed against this decision.

IX. With its reply to the statement setting out the grounds of appeal, the patent proprietor (respondent) submitted six sets of claims as its main request and auxiliary requests I to V.

(a) The **main request** is identical to former auxiliary request I held allowable by the opposition division (see points IV. and VI. above).

(b) **Auxiliary requests I to V** are identical to former auxiliary requests II to VI filed in the proceedings before the opposition division (see point IV. above).

(c) The independent claims in all the requests are identical in their wording to independent claims 1, 12 and 13 as granted (see points II. and IV. above). In auxiliary request V, they are numbered 1, 9 and 10.

(d) Dependent claim 10 of the main request reads as follows:

"***10.*** *The dosage form of claim 1, wherein the ratio of the amount of opioid agonist to the amount of opioid antagonist is in a weight ratio of from 1:1 to 50:1, from 1:1 to 20:1, or from 1:1 to 10:1.*"

Claim 10 in auxiliary requests I, II and III and claim 9 in auxiliary request IV are identical to dependent claim 10 of the main request. Auxiliary request V does not contain this claim.

X. Oral proceedings were held on 14 December 2020 in the absence of the respondent, in accordance with Rule 115(2) EPC and Article 15(3) RPBA.

XI. The appellant's arguments may be summarised as follows.

Added subject-matter

Dependent claim 10 of the main request specified ratios of opioid agonist to opioid antagonist in the dosage form, but without mentioning that only the "substantially non-releasable" form of the opioid

antagonist was to be considered in their calculation. The claim differed in this respect from the original disclosure on page 26, lines 18 to 23, in the earlier application No. 01909086.9 (Article 76(1) EPC).

Claim 1 also covered dosage forms containing an additional amount of opioid antagonist in a releasable form, as envisaged in paragraph [0056] of the description, *inter alia*. There was thus no basis for concluding, as the respondent did, that the amount of opioid antagonist mentioned in claim 10 could only mean the substantially non-releasable amount defined as mandatory in claim 1.

Sufficiency of disclosure

The person skilled in the art would not be able to put into practice embodiments of the claimed subject-matter across the scope claimed without the undue burden of having to carry out a new research programme based on trial-and-error experimentation:

The examples in the patent in suit relied mainly on naltrexone as the opioid antagonist. The patent gave no guidance on how to convert dosages and ratios of naltrexone into bioequivalent formulations when a different opioid antagonist was to be used.

Certain examples were not in conformity with claim 1 but were not marked as being "reference" examples. This cast doubt on the validity and relevance of the remaining examples.

The claims encompassed variations which might involve a considerable number of choices regarding the galenic formulation.

Furthermore, the scope of the claims was ill-defined on account of the functional feature "substantially non-releasable". Since the patent in suit did not

provide a single, binding definition of this term, the person skilled in the art was not able to identify the technical measures necessary for implementing the claimed subject-matter. It was conceded that the skilled person could carry out the "core" teaching of the patent, as far as dosage forms were concerned which entirely prevented the release of the opioid antagonist when administered intact. However, there appeared to be a large grey area of embodiments permitting some release of the opioid antagonist.

The patent described, for instance, a dosage form releasing up to 25% of the opioid antagonist within one hour of oral administration (see paragraph [0025] of the description). Alternatively, the ratio of the amount of antagonist contained in the intact dosage form to that released from the intact dosage form after one hour, determined in a specified *in-vitro* dissolution test, was at least 4:1 (paragraph [0022]), or the amount released was less than an amount that was bioequivalent to 0.25 mg naltrexone (paragraph [0023]).

As a consequence, the skilled person could not be certain to what extent claim 1 covered dosage forms providing release of the opioid antagonist upon oral administration, and whether a broad interpretation of the term "substantially non-releasable" might affect the meaning of the feature "unavailable to be absorbed", which was also present in claim 1. The uncertainty in this regard amounted to more than just a lack of clarity.

Novelty

Claim 1 must be construed to be consistent with the release characteristics mentioned in the description. Based on the broad interpretation of the term "substantially non-releasable" warranted by

paragraph [0025] of the patent in suit, the dosage form of claim 1 could not be distinguished from a dosage form releasing both the opioid agonist and the opioid antagonist in a controlled manner, as disclosed in prior-art documents D1 and D2.

Specifically, these documents referred to conventional controlled-release or sustained-release dosage forms, including matrix forms (D1: page 20, lines 16 to 21; D2: page 23, lines 6 to 10). Release rates of up to 25% at one hour after administration, as in the embodiment according to paragraph [0025] of the patent in suit, were typical for such formulations. This was evident in the prior art relating to slow-release formulations, which disclosed ranges of release rates having a large overlap with this embodiment.

The subject-matter of claim 1 was also anticipated by further passages, which were identical in D1 and D2, describing the use of a melt-extruded matrix material (see D1: page 35, lines 17 to 24; D2: page 38, lines 5 to 11).

The wording of claim 1 did not rule out dosage forms that provided the opioid agonist and the opioid antagonist in the same sustained-release matrix. The description proposed the same hydrophobic materials for formulating the opioid agonist and the opioid antagonist, such as ethylcellulose (see paragraphs [0109] and [0134] to [0136]). Moreover, hydrophobic materials mentioned in D1 and D2 were the same as those mentioned in the patent in suit.

Documents D1 and D2 further disclosed pellets and granules as defined in independent claims 9 and 10 of auxiliary request V (D1: page 34, lines 1-2; page 31, lines 18 to 27 and page 32, lines 11 to 18; identical

passages in D2: page 36, lines 19 to 20; page 34, lines 6 to 15 and page 34, line 30 to page 35, line 2).

Inventive step

Document D3 represented the closest prior art. The opposition division had correctly stated the objective technical problem as that of providing an alternative dosage form. Choosing a matrix form with a hydrophobic material would have appeared obvious to the skilled person in light of the teaching of document D14, a textbook on pharmaceutics. Section G of D14 (pages 590 to 592) showed that the person skilled in the art would have been familiar with osmotically controlled delivery systems such as that described in D3. When seeking an alternative system which was easy to manufacture, the skilled person would have chosen a conventional matrix system of the type discussed in document D14 in section E (pages 586 to 589). D14 taught that very slow sustained-release rates could be obtained with matrix systems (last paragraph on page 588). This would render the opioid antagonist "substantially non-releasable" within the meaning of claim 1. The skilled person would also have taken into consideration the teaching relating to matrix systems in documents D1 and D2 (applications in the same field of technology, with objectives similar to those of the patent in suit).

XII. The respondent's arguments (as presented in writing) may be summarised as follows.

Added subject-matter

Because claim 10 of the main request was dependent on claim 1, it was evident that the definition of the ratios in claim 10 must be based on the amount of opioid antagonist in substantially non-releasable form as defined in point (ii) of claim 1. This was in line

with the disclosure of the earlier application No. 01909086.9.

Sufficiency of disclosure

It was not in dispute that the patent in suit showed how the invention could be carried out with naltrexone. The opponent had not provided a serious reason, substantiated by verifiable facts, to doubt that the skilled person would not be able to implement the invention with a different opioid antagonist.

The patent provided a definition of the term "an opioid antagonist in a substantially non-releasable form" (paragraph [0046]), an *in-vitro* test reflecting drug release after oral administration, and numerous examples for preparing sequestered forms of opioid antagonists and dosage forms conforming to the claims. In examples 17 to 19 (reporting on studies with opioid-dependent or normal subjects), the patent also taught how it could be determined whether a co-administered amount of antagonist impaired the efficacy of the opioid.

The skilled person would have no difficulty in preparing dosage forms which entirely prevented the release of the opioid antagonist upon oral administration. While it was thus not even necessary to determine critical limits for the release of each antagonist to put the invention into practice, doing this would, in any case, only involve routine work. It was not an undue burden to identify equiantagonistic doses of different opioid antagonists either.

Novelty

The claimed dosage form was designed to release and deliver the opioid agonist to a user in order to provide analgesia. The agonist could, conceptually, not

be incorporated into the matrix of the antagonist composition, as this would prevent its release.

In contrast to the dosage forms of the invention, the dosage forms of D1 and D2 did not contain the antagonist in a sequestered form. They were designed to release both the opioid agonist and the opioid antagonist together upon oral administration.

Inventive step

The claimed invention resulted in more than a mere alternative to the dosage forms of D3 since the dosage form of claim 1 provided improved abuse deterrence. This was because it was harder to locate the opioid agonist based on the product's outward appearance.

Whether the objective technical problem was to provide an improved or an alternative dosage form, in either case the person skilled in the art would have had no incentive to abandon both the mode of operation and the structural features taught in document D3.

D3 was about osmotic dosage forms only and did not suggest at any point that the opioid antagonist should be sequestered in a matrix comprising a hydrophobic material to render it substantially non-releasable.

The teaching of documents D1, D2 and D14 regarding controlled-release formulations would not have guided the person skilled in the art to the claimed dosage forms either. The appellant's contentions in that respect were based on hindsight. As the content of these secondary documents was unrelated to the teaching and objectives of document D3, the skilled person would not have consulted them.

XIII. The appellant (opponent) ***Krka, d.d., Novo mesto*** requested that the decision under appeal be set aside and that the patent be revoked.

XIV. The respondent (patent proprietor) ***EURO-CELTIQUE S.A.*** requested that the appeal be dismissed,

or in the alternative, that the patent be maintained in amended form on the basis of one of the sets of claims filed as auxiliary requests I to V with the reply to the statement setting out the grounds of appeal.

Reasons for the Decision

1. The patent in suit

1.1 As set out in the patent in suit, opioid agonists were known and were employed as analgesics in medicine. Pharmaceutical dosage forms containing opioid agonists may be tampered with, e.g. by mechanical, thermal and/or chemical manipulation, in order to make the opioid agonists available for inappropriate use. The patent seeks to reduce the abuse potential associated with these medicines by providing tamper-resistant oral opioid agonist formulations (see paragraphs [0001], [0011] to [0018] and [0061] of the description).

1.2 To that end, the oral dosage forms according to claim 1 contain, in addition to the opioid agonist drug, an opioid antagonist compound that is rendered substantially non-releasable by dispersal in a matrix comprising a hydrophobic material.

1.2.1 When the intact dosage form is administered orally, only the opioid agonist will be released, while the opioid antagonist sequestered in the matrix composition remains unavailable to be absorbed during its transit through the gastrointestinal system, and does not block the therapeutic benefit of the opioid agonist.

1.2.2 In contrast, if the dosage form is subjected to tampering activities which compromise the integrity of the opioid antagonist matrix composition, such as crushing or grinding, the antagonist will become available to be absorbed, thus attenuating the effects of the opioid agonist and frustrating drug abuse.

1.3 Opioid antagonist matrix compositions as such are also claimed independently.

2. Added subject-matter (Article 76(1) EPC)

2.1 The earlier application No. 01909086.9 (see point I. above) specifies that in certain embodiments, the weight ratio of opioid agonist to "opioid antagonist, present in a substantially non-releasable form" is in the range of 1:1 to 50:1, 1:1 to 20:1 or 1:1 to 10:1 (see page 26, lines 18 to 23; also page 14, line 31 to page 15, line 11). The weight is that of the active ingredients.

2.2 Claim 10 of the main request (see point IX. above) recites the same ranges of 1:1 to 50:1, 1:1 to 20:1 and 1:1 to 10:1, but refers to the weight ratio of opioid agonist to opioid antagonist without the qualification "present in a substantially non-releasable form".

2.3 Provided that the entire amount of opioid antagonist in the dosage form of claim 10 is necessarily in substantially non-releasable form, claim 10 would find an adequate basis in the text passages of the earlier application. This is, however, not the case: the patent envisages embodiments additionally containing certain amounts of releasable opioid antagonist (see point 2.3.1 below), and such embodiments are not excluded by the definition of the claims (see point 2.3.2 below).

2.3.1 According to paragraph [0056] of the patent in suit,

"In certain embodiments of the present invention, the oral dosage form further comprises an opioid antagonist in a releasable form and is *[sic]* thus capable of being released from the oral dosage form when orally administered, the ratio of the opioid agonist to the releasable form of the opioid antagonist being such that the dosage form, when administered orally, is analgesically effective."

2.3.2 Independent claim 1 (see point II. above) defines a dosage form with the mandatory technical feature that an opioid antagonist in substantially non-releasable form, dispersed in a matrix, must be present.

Claim 1 uses the term "comprising" ("an oral dosage form comprising...") when listing the components of the dosage form. This implies that, apart from the mandatory components (i) and (ii) specified in the claim, further components may optionally be present. Such a further component may be an opioid antagonist in releasable form.

Thus, claim 1 does not require the total amount of opioid antagonist present in the dosage form to be in substantially non-releasable form. No such restriction can therefore be derived from the mere back-reference of dependent claim 10 to claim 1.

Claim 10 itself refers to "the ratio of the amount of opioid agonist to the amount of opioid antagonist". As "opioid antagonist" is mentioned without the definite article and only in a general way, it cannot be inferred from the language of claim 10 that this term is restricted to "the" opioid antagonist in component (ii) of claim 1 (i.e. the mandatory substantially non-releasable amount).

Neither the wording of claim 1 nor that of claim 10 therefore provides a basis for concluding that the amount of opioid antagonist in claim 10 only includes the substantially non-releasable opioid antagonist defined in claim 1.

2.4 For these reasons, the board has come to the conclusion that the scope of claim 10 also covers the embodiment mentioned in paragraph [0056] of the patent specification, which in addition to the mandatory substantially non-releasable opioid antagonist includes a certain amount of releasable opioid antagonist.

2.5 Thus, the amount of opioid antagonist for calculating the weight ratio according to claim 10 is the total amount of antagonist including any releasable amount present. Since the weight ratios according to the earlier application were based on the amount of substantially non-releasable opioid antagonist rather than the total amount, the definition of the ratios in claim 10 of the main request extends beyond the content of the earlier application as filed.

2.6 This conclusion applies equally to claim 10 of each of auxiliary requests I, II and III and claim 9 of auxiliary request IV, since these claims are identical to claim 10 of the main request (see point IX.(d) above).

2.7 For this reason, the main request and auxiliary requests I to IV are not allowable under Article 76(1) EPC.

2.8 The objection under Article 76(1) EPC does not apply to auxiliary request V, which does not contain the dependent claim at issue (see point IX.(d) above).

3. Sufficiency of disclosure (Article 83 EPC)

3.1 The claims of auxiliary request V define products, namely a dosage form or a composition. These claims are not directed to a medical use as provided for in Article 54(5) EPC and do not contain functional technical features concerning analgesic efficacy or effective abuse prevention and nor do they define a requirement for bioequivalence with naltrexone.

Thus, the issues of potency and bioequivalence raised by the appellant (see point XI. above) are not reflected anywhere in the wording or features of the claims. They are, therefore, not relevant to the subject of sufficiency of disclosure of the claimed subject-matter and need not be considered.

This is irrespective of the fact that dosage optimisation is, in any case, routine work for the galenic formulator, and establishing bioequivalence with naltrexone is not a necessary prerequisite for preparing products conforming to claims 1, 9 or 10 based on different antagonists.

3.2 The independent claims nevertheless do contain several functional definitions. These relate to the pharmacologically active agents (defined as belonging to the functional classes of "opioid agonists" and "opioid antagonists") and to the properties of the matrix (which must render the opioid antagonist "substantially non-releasable" and "unavailable to be absorbed").

3.3 The question to be answered with regard to sufficiency is whether the skilled person would be enabled to prepare the dosage form and the opioid antagonist compositions defined in the claims on the basis of the information provided in the patent in suit and taking

into account the common general knowledge on the effective filing date.

3.4 It was not in dispute that opioid agonists and antagonists were well known in the art and that suitable compounds are listed in the patent in suit (see paragraphs [0057], [0086] and [0094], and the corresponding passages of the application as filed).

3.5 Numerous embodiments of dosage forms and antagonist compositions described in the examples can be readily identified to be in accordance with the claims with regard to their components and their structural design as matrix forms. Examples 23 and 24 also show how the dissolution properties of intact and crushed opioid antagonist pellets can be tested. Beyond that, it is not necessary to describe a multitude of galenic variations (e.g. regarding the choice of excipients or the optimisation of component ratios) since such variations are accessible to the skilled person by routine modification.

3.6 It was not in dispute that the skilled person would be able to formulate matrix opioid antagonist compositions (ii) which entirely prevent the release of the opioid antagonist when orally administered.

The appellant argued, however, that the scope of the term "substantially non-releasable" was ill-defined and it could not be determined to what extent a release of the antagonist from the matrix composition upon oral administration was acceptable (see point XI. above). According to the appellant, these concerns were based in particular on the fact that paragraphs [0022] to [0025] of the patent in suit gave rise to contradictory and quite broad interpretations of the

term "substantially non-releasable" and the resulting release properties of the dosage form.

3.7 This argument cannot succeed, since claim 1 specifies not only that the matrix of the opioid antagonist composition renders the antagonist "substantially non-releasable" when the dosage form is administered orally intact, but also that the antagonist is "unavailable to be absorbed during its transit through the gastrointestinal system". This functional definition of the opioid antagonist matrix composition, together with the requirement that a hydrophobic material must be used, is deemed to be sufficiently clear for the skilled person seeking to implement the claimed subject-matter.

3.8 The board sees no reason why divergent definitions of dosage forms in the description should affect the scope of the claims, especially in light of the following considerations:

3.8.1 It is evident that the patent specification mentions multiple embodiments which are not necessarily in accordance with the current claims, and this includes the embodiments in paragraphs [0022] to [0025].

Claim 1 and each of paragraphs [0022] to [0025] provide different definitions of oral dosage forms. For the dosage forms of paragraphs [0022] to [0025], a certain proportion of release of the opioid antagonist from the intact dosage form appears to be acceptable (see also point XI. above). These definitions notably differ from that of claim 1 by not including the limiting feature "unavailable to be absorbed".

The obvious inference is that they concern unrelated embodiments, rather than that the scope of claim 1 must

forcibly be construed to cover the dosage forms of paragraphs [0022] to [0025].

Thus, embodiments in the description which are not encompassed by the subject-matter as defined by the claims cannot alter the scope of the claims and are therefore of no relevance in the assessment of patentability.

3.8.2 This conclusion is further supported by the application history of the patent:

The earlier application No. 01909086.9 (the "grandparent" application, see point I. above) contained multiple independent claims defining separate embodiments of oral dosage forms, which were not restricted to matrix-type compositions of the sequestered opioid antagonist. The definitions of these claims were duplicated in the description (see independent claims 1 to 9, 41 and 54 and the corresponding passages on page 5, line 33 to page 8, line 35 of the earlier application as filed).

The description of divisional application No. 10011789.4 as filed is identical to the description of the grandparent application, but additionally includes several pages of "embodiments" which correspond to the 61 claims of the grandparent application (see pages 78 to 85 of the application as filed).

Before the patent in suit was granted, these additional pages were dropped, but the description was not otherwise adapted to conform with the claims as granted. The granted version of the description therefore contains passages relating to subject-matter that is no longer claimed. In particular, paragraphs [0022] to [0025] of the patent in suit correspond to independent claims 4 to 7 of the grandparent

application, whereas claim 1 as granted is based on independent claim 9 of the grandparent application.

3.9 For these reasons, the claimed subject-matter is disclosed in a manner sufficiently clear and complete to be carried out by a person skilled in the art.

4. Novelty (Articles 52(1) and 54(1)-(2) EPC)

4.1 The appellant cited documents D1 and D2 as anticipating the subject-matter of claims 1, 9 and 10 of auxiliary request V.

4.1.1 Both relate to oral dosage forms comprising an opioid agonist and an opioid antagonist. The antagonist is present in the dosage form to prevent drug abuse via the parenteral route (D1) or the oral route (D2).

To achieve this, D1 claims dosage forms in which the opioid agonist and antagonist are only extractable together from the dosage form and more than one extraction step is required to separate the opioid agonist from the antagonist. The amount of opioid antagonist included is sufficient to counteract opioid effects if both drugs are extracted together and administered parenterally (see D1: claim 1).

D2 relates to an oral dosage form containing the combination of opioid agonist and antagonist at a ratio which is analgesically effective when administered at a normal dose, but aversive in physically dependent human subjects, in particular when administered at a higher dose than the usually prescribed dose of the opioid agonist (see D2: claim 1).

4.1.2 The specific passages cited by the appellant as novelty-destroying are identical in D1 and D2 (see passages as indicated in point XI. (Novelty) above).

While neither D1 nor D2 contain specific formulation examples, the cited passages basically set out, in a general way, that the opioid agonist/opioid antagonist combination may be provided as a matrix-type controlled-release or sustained-release formulation. In certain embodiments, the matrix may comprise a hydrophobic material, may be a melt-extruded material and/or may be in the form of granules or pellets.

4.2 The appellant based its objection of lack of novelty on the argument that the definitions of claims 1, 9 and 10 also covered oral dosage forms and antagonist compositions in which the opioid antagonist was dispersed in a matrix providing a slow sustained release of the antagonist, as disclosed in the cited passages of documents D1 and D2.

4.3 This argument is not convincing, for the following reasons.

4.3.1 It is implicitly understood (and is uncontested in these proceedings) that the oral dosage form of claim 1 must be designed to release the opioid agonist in order for it to be absorbed by a patient ingesting the dosage form. The dosage form may be designed to provide an immediate release or a sustained release of the opioid agonist (see the patent in suit, paragraph [0060]).

4.3.2 In contrast, the opioid antagonist is present in a sequestered form (component (ii) of claim 1), in a matrix composition designed to impede its release when the dosage form is orally administered. This effect is expressed by the functional features "substantially non-releasable" and "unavailable to be absorbed".

By itself, the term "substantially non-releasable" might be understood to include embodiments permitting some release of the opioid antagonist from the opioid

antagonist matrix composition (ii), as long as the efficacy of the opioid agonist is not impaired. This interpretation also corresponds to the definition given in paragraphs [0046] and [0047] of the patent in suit, and may be compatible with certain embodiments which are no longer claimed (see point 3.8 above).

However, claim 1 further specifies that the antagonist is "unavailable to be absorbed during its transit through the gastrointestinal system". This additional requirement strictly limits its release in respect of time and amount, such that an uptake of effective amounts after ingestion is not possible.

As a consequence, the definition of the opioid antagonist matrix composition (ii) in claim 1 does not encompass matrix systems which provide a sustained release of the opioid antagonist, or a release of up to 25% of the antagonist within one hour of oral administration (as argued by the appellant with reference to paragraph [0025] of the patent in suit). This conclusion also applies to the compositions of independent claims 9 and 10, which are defined by reference to claim 1.

Since this is the case, the appellant's argument that D1 and D2 implicitly disclose release rates of up to 25% of the opioid antagonist does not need to be addressed.

4.3.3 It is difficult to see how the opioid agonist could be released while the opioid antagonist would remain unavailable, if both are dispersed in the same matrix. D1 and D2 do not teach at any point that the opioid antagonist should be rendered unavailable to be absorbed upon oral administration of the intact dosage form. The appellant also did not identify any specific passage in documents D1 or D2 that directly and unambiguously discloses an opioid antagonist dispersed

in a matrix rendering it unavailable to be absorbed during its transit through the gastrointestinal system. The passages in D1 and D2 relating to melt-extruded matrix materials disclose neither a specific matrix with defined properties nor its effect on the opioid antagonist.

Thus, D1 and D2 do not disclose a mandatory feature of independent claims 1, 9 and 10.

4.3.4 The appellant submitted that the hydrophobic materials to be used according to the patent in suit for the opioid antagonist composition were also used in sustained-release formulations.

However, this is not relevant since it does not lead to the conclusion that the opioid antagonist compositions of claims 1, 9 and 10 may, after all, be sustained-release formulations. As correctly pointed out by the opposition division, it is well known in the art that, depending on their amounts and how they are used in combination with other excipients, the same materials can be suitable for providing controlled release or for preventing release (see the decision under appeal, point 4.7.2.1 of the Reasons; see also D1: page 35, lines 13 to 16, setting out that release profiles can be altered by varying the amount of hydrophobic material, including additional excipients, or by the method of manufacture). The fact that the hydrophobic materials of paragraphs [0109] to [0118] of the patent may also be used in sustained-release formulations is thus compatible with the finding that the wording of claim 1 excludes sustained-release formulations from the scope claimed.

4.4 In conclusion, the subject-matter of claims 1, 9 and 10 is novel relative to the disclosure of documents D1 and D2.

5. Inventive step (Articles 52(1) and 56 EPC)

Starting point in the prior art

5.1 It was common ground that document D3 represented the closest prior art.

Like the patent in suit (see section 1 above),

- D3 seeks to provide a dosage form for an opioid designed to lessen the potential for opioid abuse (see D3: page 2, lines 10 to 13);
- D3 describes dosage forms which incorporate an opioid agonist and an opioid antagonist formulated differently from the opioid agonist, such that the antagonist is not released upon administration but is maintained in the dosage form (see D3: page 2, lines 13 to 19; claim 1; page 15, lines 4 to 23).

5.2 The dosage form of D3 is an osmotic system with a bilayered core. One layer contains the opioid agonist, the other ("push layer") comprises a push-displacement composition and the opioid antagonist. Thus, the antagonist composition is separate and distinct from the agonist composition. The bilayered core is surrounded by a semipermeable wall, which has at least one exit or aperture for releasing the opioid. When the dosage form is administered to a patient, fluid is imbibed through the semipermeable wall into the dosage form, causing the push-displacement composition to expand and push the opioid drug composition through the exit aperture (see D3: claims 1 and 8; page 3, lines 14 to 18; examples; page 14, line 13 to page 15, line 3). In this way, an opioid agonist can be administered to a patient requiring an analgesic while simultaneously maintaining an opioid antagonist in the

dosage form to prevent opioid abuse (see D3: page 15, lines 4 to 7).

Technical problem and solution

5.3 According to claim 1 of the patent in suit, the opioid antagonist is formulated in a matrix-based system, with a hydrophobic material, instead of in a push-displacement composition for an osmotic system. It was not in dispute that D3 does not disclose hydrophobic materials for its antagonist compositions.

5.4 Upon administration to a patient, the dosage form of D3 releases the opioid agonist but retains the opioid antagonist, which is not present in the opioid agonist layer adjacent to the aperture, but in the push layer. The dosage form according to claim 1 also retains the opioid antagonist, in the matrix comprising the hydrophobic material. In both cases, tampering activities which destroy the integrity of the layer or matrix containing the opioid antagonist will make the antagonist available to block the effects of the opioid agonist and frustrate drug abuse.

5.5 Thus, starting from the technical teaching of document D3, the objective technical problem is to provide an alternative oral dosage form comprising an opioid agonist and an opioid antagonist, suitable for providing effective analgesia while exhibiting a reduced abuse potential.

5.6 The respondent suggested that the objective technical problem should be defined as providing an improved dosage form since the dosage forms according to claim 1 had the advantage of improved abuse deterrence. The appellant contested this advantage.

Since the claimed subject-matter was found, in favour of the respondent, to involve an inventive step based on the technical problem of providing an alternative oral dosage form, it is not necessary to assess the merit of this further approach (which sets a higher hurdle for inventive step).

Obviousness of the solution

5.7 Starting from the teaching of document D3 and faced with the objective technical problem, the person skilled in the art would have considered the option of providing alternative osmotic systems.

5.8 Nothing in D3 suggests that the opioid antagonist should be dispersed in a matrix including a hydrophobic component. D3 teaches that the antagonist formulated in the push layer of the osmotic dosage form is not released upon oral administration. Thus, there is no need to add a hydrophobic material; on the contrary, it might even have been feared that such a measure (if considered at all) might impair the osmotic properties of the system.

5.9 The appellant conceded that the fundamental technical concept of D3 was to provide a dosage form which released the opioid agonist without releasing the antagonist (see appellant's letter dated 6 April 2020; point 5.4).

5.10 The supplementary documents D1, D2 and D14 relied on by the appellant relate to sustained-release and controlled-release dosage forms including matrix forms. As mentioned in these documents, it is well known that release can be sped up or slowed down as desired, depending on the formulation of the matrix. However, none of them teaches or suggests the principle of employing a matrix with the purpose of rendering the

compound dispersed in it substantially non-releasable so that it is unavailable to be absorbed in the gastrointestinal tract.

5.11 Thus, D1 and D2 relate neither to osmotic dosage forms nor to the principle of providing a separately formulated antagonist in the dosage form which remains unavailable on oral administration. The same is true for the section of D14 relating to matrix devices. Hence, the skilled person would have had to depart entirely from the mode of operation and technical concept of D3 to consider the supplementary documents, and furthermore would have had to change their teaching to arrive at the subject-matter of claim 1. For these reasons, the supplementary documents would not have led the skilled person to the subject-matter of claim 1.

5.12 The appellant did not substantiate its allegation that matrix forms are always easier to prepare, nor would this change the reasoning set out in point 5.11.

5.13 Independent claims 9 and 10 do not relate to dosage forms but instead define opioid antagonist compositions, namely component (ii) as defined in claim 1, with additional technical features. However, the appellant did not propose any objection involving an approach to assessing inventive step specific to claims 9 and 10.

5.14 For these reasons, the claimed subject-matter according to the claims of auxiliary request V involves an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended in the following version:

Description:
Paragraphs [0001] to [0277] of the patent specification

Claims:
Claims 1 to 10 of auxiliary request V filed with the reply to the statement setting out the grounds of appeal

Drawings:
Figures 1 to 3 of the patent specification.

The Registrar: The Chairwoman:

M. Schalow M. Pregetter

Decision electronically authenticated