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Language of the proceedings: EN

Title of invention:
BUPRENORPHINE WAFER FOR DRUG SUBSTITUTION THERAPY

Patent Proprietor:
EURO-CELTIQUE S.A.

Opponents:
Hexal AG
Orexo AB
Gallafent, Alison
ETHYPHARM

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

Keyword:
Inventive step - (no)
Auxiliary requests - held inadmissible (yes)

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Case Number: T 0632/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 2 December 2019

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 4 February 2016 revoking European patent No. 2059243 pursuant to Article 101(2) and Article 101(3)(b) EPC**

Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
M. Blasi

Summary of Facts and Submissions

I. European patent No. 2 059 243 (the patent in suit) was granted with a set of ten claims.

II. Four oppositions were filed against the patent in suit, opposing it under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. The patent proprietor requested that the oppositions be rejected (main request) and filed amended sets of claims of auxiliary requests I and II, Ia and IIa, and III to VI, *inter alia*.

The claims of auxiliary requests I and II were presented with a letter dated 30 September 2015, i.e. two months before the date of the oral proceedings before the opposition division. The claims of auxiliary requests Ia, IIa and III to VI were first submitted during the oral proceedings before the opposition division. All other auxiliary requests were withdrawn (see the decision under appeal, point 9.2).

Independent claims 1, 7 and 8 of **auxiliary request Ia** read as follows:

"1. Oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof, said dosage form being a non-gelatin polymeric film comprising a matrix which is formed from at least one matrix-forming polymer and in which said buprenorphine or said pharmaceutically acceptable salt thereof is dissolved or homogenously dispersed,

wherein said at least one matrix-forming polymer is a cellulose ether selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC) and carboxymethylcellulose (CMC),

and wherein the dosage form releases substantially all of said buprenorphine or said pharmaceutically acceptable salt thereof within less than 2 minutes after oral, preferably sublingual, application of the dosage form.

7. Use of an oral pharmaceutical dosage form according to any of claims 1 to 6 in the manufacture of a medicament for treating pain.

8. Use of an oral pharmaceutical dosage form according to any of claims 1 to 6 in the manufacture of a medicament for drug substitution therapy."

Claim 1 of **auxiliary request IIa** reads as follows (the differences by comparison with claim 1 of auxiliary request Ia are underlined):

"1. Oral pharmaceutical dosage form comprising buprenorphine or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio of from 1:1 to 10:1,

said dosage form being a non-gelatin polymeric film comprising a matrix which is formed from at least one matrix-forming polymer and in which said buprenorphine or said pharmaceutically acceptable salt thereof, and said naloxone or said pharmaceutically acceptable salt thereof, are dissolved or homogenously dispersed,

wherein said at least one matrix-forming polymer is a cellulose ether selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), hydroxyethylmethylcellulose (HEMC),

hydroxyethylcellulose (HEC), methylcellulose (MC) and carboxymethylcellulose (CMC),

and wherein the dosage form releases substantially all of said buprenorphine or said pharmaceutically acceptable salt thereof and said naloxone or said pharmaceutically acceptable salt thereof within less than 2 minutes after oral, preferably sublingual, application of the dosage form."

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

D2: WO 98/26780 A2
D5: WO 03/003957 A1
D6: Drug and Alcohol Dependence 50, 1-8 (1998)
G18: Suboxone® Data Sheet (21 March 2006)

V. The decision under appeal is the decision of the opposition division revoking the patent, announced on 1 December 2015 and posted on 4 February 2016.

According to the decision under appeal,

- The subject-matter of claim 1 of the patent as granted (main request) lacked novelty.
- An independent claim present in both auxiliary requests I and II contained added subject-matter. Auxiliary requests Ia and IIa, which differed from auxiliary requests I and II in that they no longer contained the objectionable claim nor the claims referring back to it, were admitted into the proceedings.
- Starting from the teaching of document D5, which disclosed a buprenorphine film composition and film-forming polymers, the person skilled in the art seeking to obtain films with a suitable release time of buprenorphine would have arrived at the

subject-matter of claim 1 of auxiliary request Ia without exercising inventive skill.

- Document D2, which related to drug substitution therapy and envisaged combining buprenorphine with naloxone, represented the prior art closest to claim 1 of auxiliary request IIa. The partial technical problems to be solved were (i) to determine a suitable ratio of buprenorphine to naloxone, and (ii) to obtain buprenorphine films with a suitable release time. Since suitable matrix materials were known from document D5, and the appropriate ratio of buprenorphine to naloxone was well known, e.g. from G18 describing a commercial product, the subject-matter of claim 1 of auxiliary request IIa did not involve an inventive step.
- Auxiliary requests III to VI were not admitted into the proceedings since, *prima facie*, the claims of the new requests did not address the objection regarding lack of inventive step and raised new issues under Articles 84 and 123(2) and (3) EPC.

VI. The patent proprietor (appellant) filed an appeal against this decision, its main request being that the oppositions be rejected.

With the statement setting out the grounds of appeal, the appellant submitted nine sets of claims as its main request and auxiliary requests Ia, Ia-1, Ia-2, Ia-3, IIa, IIa-1, IIa-2 and IIa-3. The appellant subsequently withdrew the main request and auxiliary requests Ia-1, IIa-1, IIa-2 and IIa-3 (see points VII. and VIII. below).

The claims of **auxiliary request Ia** and **auxiliary request IIa** are identical to those of auxiliary

requests Ia and IIa considered in the decision under appeal (see point III. above).

Claim 1 of **auxiliary request Ia-2** reads as follows (the differences by comparison with claim 1 of auxiliary request Ia are underlined):

"1. Oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof for use in drug substitution therapy,

said dosage form being a non-gelatin polymeric film comprising said buprenorphine or pharmaceutically acceptable salt thereof,

wherein said dosage form can be formed by dissolving or homogenously dispersing said buprenorphine or pharmaceutically acceptable salt thereof in a hydrophilic organic system which is applied to a non-gelatin polymeric film substrate, the film substrate being based on

a cellulose ether selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC) and carboxymethylcellulose (CMC),

and wherein the dosage form releases substantially all of said buprenorphine or said pharmaceutically acceptable salt thereof within less than 2 minutes after oral, preferably sublingual, application of the dosage form."

Claim 1 of **auxiliary request Ia-3** reads as follows (the differences by comparison with claim 1 of auxiliary request Ia are underlined):

"1. Oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof for use in drug substitution therapy,

said dosage form being a non-gelatin polymeric single discrete film comprising said buprenorphine or pharmaceutically acceptable salt thereof,

wherein said film can be formed by dissolving or homogenously dispersing said buprenorphine or pharmaceutically acceptable salt thereof in a hydrophilic organic system which is applied to a non-gelatin polymeric film substrate, the film substrate being based on

a cellulose ether selected from the group consisting of hydroxypropylmethylcellulose (HPMC), hydroxypropyl-cellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC) and carboxymethylcellulose (CMC),

and wherein the dosage form releases substantially all of said buprenorphine or said pharmaceutically acceptable salt thereof within less than 2 minutes after oral, preferably sublingual, application of the dosage form."

VII. By letter of 25 November 2019, the appellant withdrew its main request.

VIII. Oral proceedings (scheduled in conformity with the parties' requests) were held on 2 December 2019 in the absence of respondent-opponent 2 and respondent-opponent 3, which had been duly summoned and, in accordance with Article 15(3) RPBA, were treated as relying only on their written case.

During the oral proceedings, the patent proprietor withdrew auxiliary requests Ia-1, IIa-1, IIa-2 and IIa-3.

IX. The appellant's arguments may be summarised as follows:

Inventive step - auxiliary request Ia

Document D2 should be regarded as the closest prior art. The dosage form according to claim 1 of auxiliary request Ia differed from the film compositions envisaged in document D2 on account of the specified release time of buprenorphine, the matrix-forming polymer and on account of the further distinguishing feature that the film only consisted of a single layer, as confirmed by paragraphs [0055] and [0057] of the patent in suit. The technical problem to be solved was the provision of an oral dosage form of buprenorphine that was less prone to abuse.

The achievement taught in D2 was the direct contact of a large diffusion area with the oral mucosa, which made it more difficult for an abuser to remove the preparation from the mouth and which improved the bioavailability of buprenorphine by reducing the portion of the drug that was swallowed. The films according to D2 provided a disintegration time of a few minutes (D2: page 6, line 4). Cellulose ethers were not disclosed as matrix-forming polymers but rather as additives providing mucoadhesion (D2: page 6, second paragraph). Furthermore, D2 suggested a bilayered or multilayered structure of the dosage form for embodiments using mucoadhesive excipients.
The teaching of D2 alone could thus not lead to the claimed subject-matter.

The person skilled in the art would have had no reason to combine the references D2 and D5, in particular as D5 did not relate to drug substitution therapy. Even taking D5 into account, the skilled person would not have derived from it an incentive to choose the specific structure and composition of the dosage form

defined in claim 1. The entire disclosure of document D5 related to multi-layer dosage forms, teaching which led away from a single-film design as defined in claim 1. Moreover, on the basis of the data provided in D5 it was not possible to predict the actual disintegration or dissolution properties of films containing buprenorphine in a cellulose ether matrix. Hence, the teaching of D5 would not have given the skilled person a reasonable expectation of success in attaining rapid release times of less than two minutes.

Admission of auxiliary requests Ia-2 and Ia-3

Auxiliary requests Ia-2 and Ia-3 represented a legitimate attempt by the appellant to react to the issues set out in the decision under appeal. The relevance of the question of whether the claimed scope was restricted to single-layer films had become clear for the first time during the oral proceedings before the opposition division and in the decision under appeal. The appellant had reacted during the oral proceedings by filing auxiliary requests III to VI, which had subsequently been rejected, not for introducing the concept of a single-layer film at a late stage in the proceedings, but for other reasons. The minutes of the oral proceedings before the opposition division (points 14.4 to 15.2) showed that the issue of claim construction (single layer *vs.* multilayer) had first been discussed in relation to auxiliary request IIa. In the reasoning given in the decision under appeal (point 21.7) that issue, however, already arose in relation to auxiliary request Ia.

The claims of auxiliary requests Ia-2 and Ia-3 were convergent with the higher-ranking auxiliary request Ia in that they merely made it clear that the claimed dosage form was restricted to single-layer embodiments.

Inventive step - auxiliary request IIa

Concerning the inventive step of claim 1 of auxiliary request IIa, the same arguments applied as in the case of claim 1 of auxiliary request Ia.

X. The respondents' arguments may be summarised as follows:

Inventive step - auxiliary request Ia

Document D2 taught that buccal or sublingual delivery of buprenorphine from a fast-releasing dosage form was advantageous both in the treatment of pain and in drug substitution therapy. The dosage form according to claim 1 differed from the film compositions envisaged in document D2 on account of the specified release time of buprenorphine and the structural features of the film. The objective technical problem consisted in attaining rapid release from buprenorphine-containing films as addressed in D2. The person skilled in the art seeking to solve that technical problem would have consulted documents relating to known technologies for rapid release, and in particular document D5 which related to quick-dissolving oral mucosal drug delivery preparations. D5 disclosed cellulose ether matrix materials suitable for attaining rapid release which were identical to the materials mentioned in claim 1. Thus, the person skilled in the art would have arrived at the subject-matter of claim 1 without exercising inventive skill.

Admission of auxiliary requests Ia-2 and Ia-3

The question of whether the definition of the claimed dosage form covered multilayer films had been discussed at length in the oral proceedings before the opposition division, in the context of inventive step and the appellant's argument that documents D2 and D5 both

related to multilayered films. Auxiliary requests Ia-2 and Ia-3, intended by the appellant to restrict the claimed scope to single-film compositions, therefore could and should have been filed during the proceedings before the opposition division. Moreover, the subject-matter defined in auxiliary requests Ia-2 and Ia-3 diverged from that of the higher-ranking auxiliary request Ia since the new requests were based on a different embodiment incorporating different technical features.

Inventive step - auxiliary request IIa

While document D2, on page 7, proposed combination products containing both buprenorphine and naloxone for drug substitution therapy, it did not indicate a ratio between the two drugs. Defining a suitable ratio of buprenorphine to naloxone could thus be regarded as a further partial technical problem, in addition to the problem of providing rapid-release film compositions. It was however known, e.g. from documents D6 and G18, that a ratio of 4:1, which was within the range defined in claim 1 of auxiliary request IIa, was suitable.

XI. The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the claims of one of auxiliary requests Ia, Ia-2, Ia-3, IIa, all enclosed with the statement setting out the grounds of appeal.

XII. Respondent-oppponent 1, respondent-opponent 2 (in its written submissions) and respondent-opponent 4 requested that the appeal be dismissed.

Within the purview of this request, they also requested that auxiliary requests Ia-2 and Ia-3 not be admitted into the proceedings pursuant to Article 12(4) RPBA.

XIII. Respondent-opponent 3 did not submit any substantive comment or request in the course of the appeal proceedings.

Reasons for the Decision

1. Admissibility of the appeal

The appeal complies with Articles 106 to 108 EPC and Rule 99 EPC and is admissible.

2. Inventive step - auxiliary request Ia

Patent in suit

2.1 The patent in suit relates to dosage forms of buprenorphine that are useful in drug substitution therapy. It is mentioned that sublingual administration is the preferred route of administration of buprenorphine. Sublingual tablets containing buprenorphine alone (Subutex®) or in combination with naloxone (Suboxone®) were state of the art and commercially available. These tablets typically disintegrate over a period of five to ten minutes (see paragraphs [0008] to [0010], [0012] and [0027] of the patent in suit).

2.2 Drug addicts may try to divert sublingual buprenorphine tablets by removing them from the mouth and later selling them or isolating the buprenorphine to apply it parenterally. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in an opioid addict will lead to serious withdrawal symptoms (see the patent in suit, paragraphs [0011] and [0012]).

2.3 The patent in suit (see paragraph [0013]) identifies a need for further dosage forms of buprenorphine which are resistant to diversion and/or abuse and which can be used for drug substitution therapy, but which may also provide efficient analgesia in cases where the preparation is administered to alleviate pain in a patient.

2.4 The solution to that problem suggested in the patent in suit is the provision of a rapid-release dosage form suitable for sublingual administration, in the form of a film based on a matrix-forming polymer which is a specific cellulose ether. It is desired that buprenorphine should be released from the dosage form in less than two minutes.

Starting point in the prior art

2.5 It was common ground that the disclosure of document D2 was a suitable starting point in the prior art for the assessment of inventive step.

2.6 Document D2 relates to flat dosage forms for the administration of buprenorphine in the oral cavity and to the oral mucosa (see D2: first paragraph).
D2 discusses sublingual tablets containing buprenorphine which were commercially available as Temgesic® at the time of writing. According to D2, compressed tablets have long disintegration times of five to ten minutes. This is a drawback for patients receiving treatment for acute pain, and it also facilitates drug diversion by patients receiving drug substitution therapy (see D2: page 3, last paragraph to page 4, line 23).

2.7 D2 seeks to provide dosage forms which release buprenorphine in the oral cavity without the disadvantages of the sublingual compressed tablets of

the prior art (see D2: paragraph bridging pages 4 and 5). Thus, D2 starts from the same situation and is concerned with the same general technical problem as the patent in suit.

2.8 The technical solution according to D2 (see page 5, second paragraph) is a flat, film-like or paper-like dosage form which is applied to be in contact with the oral mucosa. This dosage form may be prepared by casting a film from a mixture comprising the drug, a solvent and a water-soluble film-forming polymer, or by thermoplastic moulding of a mixture comprising the drug and a thermoplastic film-forming polymer (see D2: claim 1 and page 9, line 8 to page 10, line 11).

2.9 Document D2 discloses cellulose ethers (such as methyl cellulose and carboxymethyl cellulose) as materials which may provide mucoadhesive properties to the dosage form (see D2: page 6, second paragraph).

Technical problem and solution

2.10 The subject-matter of claim 1 according to auxiliary request Ia differs from the disclosure of document D2 in that it requires the release of substantially all of the active agent (i.e. buprenorphine or a salt thereof) within less than two minutes after administration and further specifies that the dosage form is a polymeric film comprising a matrix in which the active agent is dissolved or homogeneously dispersed, and in which at least one matrix-forming polymer is a specific cellulose ether.

2.11 The film-type product according to claim 1 provides an oral dosage form ensuring the rapid release of buprenorphine. The release time of "less than two minutes" is indicated in the claim as a desideratum.

2.12 The patent itself does not define the concept of a release time but refers instead to the disintegration time, as in paragraph [0054]:

> *"Thus, the person skilled in the art will have to ensure that indeed an oral dosage form is used which is able to allow for incorporation of sufficient amounts of buprenorphine and preferably also of naloxone and which at the same time disintegrates rapidly enough to release the active agents instantly"*.

It is general knowledge that drug release means that the dosage form has disintegrated and the drug contained therein has dissolved or dispersed.

The patent in suit mentions that fast-dissolving or rapidly disintegrating pharmaceutical dosage forms and formulating principles for providing such forms were well known in the art (see paragraphs [0037] and [0038] of the patent and page 8, lines 10 to 14 of the application as filed).

While the patent in suit provides neither formulation examples nor technical data for specific embodiments of the claimed dosage forms, it was not in dispute that the person skilled in the art would have been capable of formulating dosage forms as defined by the structural features mentioned in claim 1 which also attained a release of substantially all of the drug in less than two minutes.

2.13 Starting from the technical teaching of document D2, the objective technical problem is thus to provide a specific fast-releasing oral mucosal dosage form of buprenorphine.

2.14 It may be assumed that the technical problem is solved by the subject-matter of claim 1.

Obviousness of the solution

2.15 Document D2, like the patent in suit, acknowledges that known sublingual compressed tablets did not provide very rapid disintegration (see D2: page 4, lines 1 to 23: "not inconsiderable disintegration times", "usually five to ten minutes" *[translation by the board]*) and that this is a disadvantage in many aspects. Specific drawbacks mentioned are the risk that a higher proportion of drug will be swallowed and thus remain ineffective, the delay of the analgesic effect in patients who require rapid pain relief, or the additional time which must be invested by medical personnel to observe subjects receiving drug substitution therapy, in order to prevent drug diversion.

A more direct and measured administration is expected from the dosage forms of D2, which permit a large surface area releasing the drug to be placed in direct contact with the oral mucosa. In this context, D2 states that "even with the simplest design according to the invention and with a disintegration time of a few minutes after application or after exposure to aqueous media, the superiority of a film containing buprenorphine over a tablet containing buprenorphine will therefore become apparent." (see D2: page 6, lines 2 to 8) *[translation by the board]*). This implies the possibility that disintegration times can also be optimised.

Even if D2 does not specify a release time, the person skilled in the art reading D2 would infer from the context of these passages that a short release time is a desirable property and that the design of the dosage forms of D2 makes it possible, in principle, to reduce release times in comparison with compressed tablets.

2.16 Thus, within the framework of the teaching of document D2, the person skilled in the art would have had an incentive to aim for low release times and would have consulted prior art concerned with fast-releasing dosage forms for application to the oral mucosas.

2.17 One such document is D5, which relates to a quick-dissolving oral mucosal dosage form. The substance to be released may be buprenorphine (see D5: claims 1 and 12; paragraphs [0002], [0028] and [0063]).

The drug-releasing layer of the dosage form according to D5 is a mucoadhesive, fast-dissolving film. Like the films according to document D2, this film may be prepared by solvent-casting or extrusion methods (see D5: paragraphs [0084] and [0086]), which would result in a matrix containing dissolved or homogeneously dispersed drug.

The film material may be chosen from various polymers including hydroxypropyl methyl cellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, methyl cellulose and carboxymethyl cellulose (see D5: paragraphs [0085], [0061] and [0062]).

Such mucoadhesive films tend to be hygroscopic, which may negatively affect storage stability; furthermore, these films may be difficult to handle given their inherent tendency to adhere to moist surfaces (see D5: paragraph [0007]).

For these reasons, the drug-releasing film is disposed between two protective non-tacky moisture-barrier coating layers comprising a non-crosslinked polymer and a moisture barrier modifier (typically a wax, solid lipid or resin; see D5: paragraph [0075]). These outer layers typically have a thickness of between 1 and 25 µm (see D5: paragraph [0033]). D5 explains that, once the dosage form is removed from

its packaging and placed on an oral mucosal surface, all or a portion of the moisture-barrier coating layers are melted and cleared away, or disintegrate rapidly, exposing the mucosal-surface-coat-forming inner layer to the oral mucosa. The remaining inner layer will hydrate substantially immediately to form a coating on the moist surface of the mucous membrane and then disintegrate or dissolve to release the active agent (see D5: paragraph [0052]).

The dosage form preferably dissolves or disintegrates in the oral cavity within 1 to 600 seconds, more preferably 1 to 60 seconds and most preferably in less than 30 seconds (see D5: paragraph [0034]).

2.18 Document D5 discloses formulation examples for the composition of the coating solution used to prepare the drug-containing film. Example 21 set out on page 25 of D5 contains buprenorphine combined with "Methocel E50" (which is a hydroxypropyl methyl cellulose) as the film-forming material.

2.19 While the time in which buprenorphine would be released from such a film is not indicated in Example 21, document D5 teaches that a specific hydroxypropyl methyl cellulose is the film-forming material preferred for these films (see D5: paragraph [0062]) and that fast release times may be achieved with hydroxypropyl methyl cellulose (HPMC).

- A film formed with "Methocel E5" (a HPMC material) and conventional additives was found to disintegrate and dissolve in well under one minute (D5: pages 17 and 18, Example 1, Tables 1 to 4).
- Thicker films made of the same material, formulated either without a drug or with various drugs, still disintegrated and dissolved in less than two

minutes (D5: pages 18 and 19, Examples 4 to 8, Tables 5 and 6).

- D5 explicitly teaches that the properties of the mucosal-surface-coat-forming inner layer may be modified by varying the individual components used therein; in particular, the dissolution rate of the film may be prolonged by using HPMC with a higher molecular weight (see D5: paragraph [0090]).
- The films according to Tables 9a and 9b of D5, all prepared according to Example 1 but with different types of HPMC, all exhibited rapid disintegration and dissolution in under two minutes.
- D5 also teaches that the moisture-barrier coating outer layers do not significantly delay the disintegration of the inner layer (see D5: paragraph [0052]; see also pages 22 and 24, Examples 10 and 15, Table 11, setting out similarly short disintegration times for a specific embodiment with or without a coating layer).

While the examples in D5 setting out disintegration and dissolution time data do not concern films containing buprenorphine as the drug, the data presented in D5 would nevertheless have been sufficient to give rise to a reasonable expectation of success, i.e. the expectation that a film based on HPMC and containing buprenorphine could be prepared which would release substantially all of the drug in under two minutes (with or without fast-disintegrating protective outer layers).

2.20 The appellant argued that the person skilled in the art would not have consulted document D5 because D5 did not relate to drug substitution therapy. In any case, the teaching of D5 led away from the claimed subject-matter, since it related to multi-layer films, while

claim 1 of auxiliary request Ia was restricted to single-layer films. The teaching of document D2 likewise led away from the claimed subject-matter since D2 mentioned that a design with two or more film layers was preferred when mucoadhesive components were used, and it did not teach that cellulose ethers were matrix-forming polymers (see D2: page 6, paragraphs 2 and 3).

2.21 The board does not reach the same conclusions.

2.21.1 Neither the objective technical problem nor claim 1 of auxiliary request Ia are restricted to the use of the dosage form in drug substitution therapy.

The person skilled in the art would have consulted D5 because it relates to fast-releasing oral mucosal dosage forms and gives formulation examples for the drug-containing layer suitable for attaining rapid drug release. This is the knowledge required and sought by the skilled person to solve the objective technical problem (see points 2.13, 2.16 and 2.17 above).

Claim 1 of auxiliary request Ia is not limited by any of its technical features to use in drug substitution therapy. Indeed independent claims 7 and 8 of this request relate to the composition of claim 1 for either pain relief or drug substitution therapy.

Thus, in any case, there is no reason why drug substitution therapy should be mentioned in D5 to make this document eligible for being consulted.

The specific circumstances of drug substitution therapy are one of the reasons why rapid release would have been desired, but this issue is already discussed in D2, which teaches that rapid release is desirable both in pain treatment and in drug substitution therapy (see D2: paragraph bridging pages 3 and 4). Document D5 focuses on the galenic formulation of the dosage form, which can be used for delivering a variety of active

agents - including buprenorphine. The relevance of the teaching in D5 regarding formulation aspects would not change if the document mentioned drug substitution therapy as one possible use of buprenorphine, or repeated the reasons why rapid release is desirable in drug substitution therapy.

2.21.2 It is readily apparent from the general teaching of D5 that the inner layer is the relevant drug-delivering layer of the dosage form and that the outer layers are added only for protection during storage and for improved handling of the tacky drug-delivering layer (see point 2.17 above). The teaching in D5 regarding suitable film-forming polymers for the drug-delivering layer is not affected by the dosage form design envisaging fast-disintegrating outer layers that may be applied to the inner layer using roller coating, spraying, dipping or laminating techniques (see D5: paragraph [0084]).

2.21.3 Document D2 mentions that carboxymethyl cellulose and methyl cellulose have mucoadhesive properties (see D2: page 6, second paragraph). If mucoadhesive materials are employed, it is preferred (but not mandatory) that the dosage form has two or more layers to prevent the preparation from making different parts of the mucosa stick together (see D2: page 6, third paragraph). Thus, the teaching of document D2 is basically consistent with that of document D5 and confirms that the additional layers have their own functionality and, depending on the circumstances, are not indispensable.

2.21.4 Contrary to the appellant's further argument, the statement in D2 (page 6, second paragraph) designating the cellulose ethers as mucoadhesive excipients ("Hilfsstoffe") does not rule out their use as matrix-

forming polymers, since carrier materials are excipients.

2.21.5 Moreover, contrary to the appellant's view, claim 1 of auxiliary request Ia does not define the claimed dosage form as an embodiment having only a single layer. It is not implicit that a polymeric film comprising a matrix in which the drug is dissolved or homogenously dispersed must consist of only one layer, since a design in which the film comprises further layers in addition to the drug-containing matrix layer is also compatible with this definition.

The appellant also referred to the description of the patent in suit in support of its interpretation of claim 1 as requiring a single-layer design. However, it is not permissible to infer new restrictions to a claim from the description. In this case, the passage relied on by the appellant (paragraphs [0055] to [0057] of the patent in suit) in fact relates to a different embodiment than that claimed (see point 3.3.3 below).

Thus, if the prior art teaches (D5) or prefers (D2) a design involving more than one layer, this teaching does not in fact lead away from the subject-matter of claim 1. Alternatively (see point 2.21.3 above), it would also appear possible to optimise the composition and properties of the matrix material (see D5: paragraph [0090]), or to handle the dosage form with an applicator (see D5: paragraph [0054]), so as to render further protective layers unnecessary. It may also be mentioned in this context that the patent in suit does not provide any formulation examples or comparative data examining the issues of hygroscopic behaviour and tackiness.

2.22 In summary, the person skilled in the art starting from the teaching of document D2 and seeking to solve the

objective technical problem would have consulted document D5 relating to rapid-releasing oral mucosal dosage forms and would have found in D5 the teaching that cellulose ethers as specified in the present claim 1, and especially HPMC, are materials suitable for attaining the desired rapid drug release from a matrix film.

2.23 As a consequence, the subject-matter of claim 1 of auxiliary request Ia does not involve an inventive step within the meaning of Article 56 EPC.

3. Admission of auxiliary requests Ia-2 and Ia-3

3.1 Auxiliary requests Ia-2 and Ia-3 were filed for the first time with the appellant's statement setting out the grounds of appeal. In accordance with Article 12(4) RPBA, the board has the power to hold inadmissible *inter alia* requests which could have been presented in the proceedings before the opposition division, even if they were presented together with the statement of grounds of appeal, relate to the case under appeal and meet the requirements of Article 12(2) RPBA.

3.2 According to the appellant, auxiliary requests Ia-2 and Ia-3 had been filed in response to an issue of claim construction which had only arisen during the oral proceedings before the opposition division (namely whether claim 1 of auxiliary request Ia was restricted to single-layer films), and the subject-matter of the new auxiliary requests was convergent with that of auxiliary request Ia. The respondents argued that the new claim requests were not convergent and should furthermore have been filed during the oral proceedings before the opposition division at the latest.

3.3 Convergence

3.3.1 Claim 1 of both requests (see point VI. above) defines a further medical use in the claim format provided by Article 54(5) EPC ("for use in drug substitution therapy"). This amendment is irrelevant to the issue of convergence as it basically corresponds to independent claim 8 of auxiliary request Ia (likewise relating to drug substitution therapy but drafted in the form of a "Swiss-type" claim; see point III. above).

3.3.2 Furthermore, claim 1 of each of auxiliary request Ia-2 and auxiliary request Ia-3 differs from the claims of auxiliary request Ia on account of the omission of the technical feature which requires the dosage form to be a non-gelatin polymeric film comprising a matrix formed from at least one polymer and in which the drug is dissolved or homogeneously dispersed.

Instead, both claims define the dosage form as a non-gelatin polymeric film comprising buprenorphine or a salt thereof. The dosage form (auxiliary request Ia-2) or the film (auxiliary request Ia-3) is further defined by its process of preparation, according to which the drug is dissolved or dispersed in a "hydrophilic organic system" which is then applied to a non-gelatin polymeric film substrate based on a cellulose ether.

Such a process will not inevitably result in the drug being dissolved or homogeneously dispersed in a matrix, since the process definition does not rule out the possibility that the drug may end up being distributed inhomogeneously in the polymeric film substrate along a concentration gradient, or deposited to some extent on the surface of the film.

Hence, the scope of claim 1 of auxiliary request Ia-2 and claim 1 of auxiliary request Ia-3 encompasses a new embodiment and for that reason it is not convergent

with the scope of the claims of auxiliary request Ia. If admitted, these requests would have opened up a fresh case.

3.3.3 In this context, it may also be mentioned that both the application as filed and the patent in suit contain several distinct passages which relate to different embodiments and technologies of oral dosage forms and of films (described *inter alia* by reference to different prior-art documents).

The claims of auxiliary request Ia correspond to the embodiment described on pages 16 to 20 of the application as filed (corresponding to paragraphs [0074] to [0097] of the patent), which requires a matrix in which the drug is dissolved or homogeneously dispersed (see the application as filed, page 17, lines 3 to 6). Indeed, the claims of all auxiliary requests considered in the decision under appeal (auxiliary requests Ia, IIa and former auxiliary requests III to VI) contain this technical feature or a similarly worded feature defining a film formed from at least one matrix-forming polymer in which the drug or drugs is/are dissolved or homogeneously dispersed.

The product-by-process feature added to claim 1 of each of the current auxiliary requests Ia-2 and Ia-3 belongs, however, to a different embodiment described on page 11, line 21 to page 13, line 2 of the application as filed (corresponding to paragraphs [0055] to [0059] of the patent in suit). This fact additionally underscores the board's finding of divergence.

Also, this latter text passage contains the only mention in the patent of a single discrete film - in the specific context of the preparation process in

which a film substrate is contacted with a solution or dispersion of the drug (see paragraph [0057]):

> *"Alternatively, the film substrate may liquefy or dissolve partly or fully during the incorporation process but nevertheless finally form a single, discrete film, after curing".*

3.4 Procedural history

3.4.1 The appellant's main request during the proceedings before the opposition division was that the oppositions be rejected. The independent claims as granted do not specify that the dosage form should be a polymeric film.

3.4.2 As summarised in the decision under appeal on page 19, the appellant, in reply to the notices of opposition, filed seven sets of amended claims as its auxiliary requests. These requests concerned combinations of granted claims.

Just before the expiry of the time limit according to Rule 116 EPC, the appellant replaced those auxiliary requests with 12 new sets of amended claims which included features taken from the description, and, in particular, most of these requests included the feature defining the dosage form as a non-gelatin polymeric film comprising a matrix which is formed from at least one matrix-forming polymer and in which the drug(s) is/are dissolved or homogeneously dispersed.

As a consequence of the appellant's filing behaviour, on the day of the oral proceedings before the opposition division none of these new requests had been previously discussed. During the oral proceedings, the appellant was given the opportunity to file new requests in response to objections raised under Article 123(2) EPC (auxiliary requests Ia and IIa) and

Article 56 EPC (former auxiliary requests III to VI) (see point III. above).

3.4.3 The issue of whether the claimed dosage form could have more than one film layer was brought up and discussed in the context of inventive step during the oral proceedings before the opposition division (see points 10.2, 14.4, 14.5, 15.1 and 15.2 of the minutes), and the opposition division expressly advised the parties of its conclusion that the wording of claim 1 of auxiliary request IIa also encompassed multilayered films (see point 16 of the minutes).

3.4.4 Since the wording of claim 1 of auxiliary request IIa is identical in this respect to that of claim 1 of auxiliary request Ia (the only difference being the mandatory presence of naloxone in a specified ratio), it is immaterial that this issue is also discussed in the decision under appeal in the context of auxiliary request Ia in addition to the identically worded assessment in the context of auxiliary request IIa (see the decision under appeal, page 16, points 21.7 and 28.9 of the Reasons). It could not have been surprising to the appellant that the same interpretation was given to an identical definition present in both requests.

3.4.5 During the oral proceedings before the opposition division the appellant filed sets of claims of new auxiliary requests III to VI to address the opposition division's finding of lack of inventive step.

In these requests, the wording "comprising a matrix" had been deleted in response to the argument that the claims were not restricted to a single-layer design (see point 16.2 of the minutes).

The opposition division did not admit auxiliary requests III to VI into the proceedings since, firstly, this amendment did not actually restrict the claimed dosage form to a single-layer design and did not *prima facie* overcome the objection of lack of inventive step, and, secondly, the requests appeared to give rise to new issues under Articles 84, 123(2) and 123(3) EPC (see point 17 of the minutes, and the decision under appeal, points 30 and 31 of the Reasons; see also point V. above).

The appellant then did not file any other requests, although it would have been possible to do so (see point 17 of the minutes).

3.5 Conclusion

3.5.1 The issue of claim interpretation, which the claims of new auxiliary requests Ia-2 and Ia-3 purportedly address, was extensively discussed in the oral proceedings before the opposition division and the appellant would have had the opportunity to file these requests at that point. It should indeed have done so, especially since the new requests related to a different and diverging embodiment of the claimed dosage form (see section 3.3 above). The filing of auxiliary requests Ia-2 and Ia-3 therefore amounted to presenting a fresh case in the appeal proceedings. This would have required the board to address new issues or remit the case to the opposition division, neither alternative being a satisfactory way to proceed in view of the primary object of the appeal proceedings to review the decision under appeal in a judicial manner.

3.5.2 For these reasons, the board held auxiliary requests Ia-2 and Ia-3 inadmissible pursuant to Article 12(4) RPBA.

4. Inventive step - auxiliary request IIa

4.1 The dosage form according to claim 1 of auxiliary request IIa differs from that defined in claim 1 of auxiliary request Ia in that it contains naloxone or a pharmaceutically acceptable salt thereof as a mandatory further component, with the weight ratio of buprenorphine to naloxone (or their salts) ranging from 1:1 to 10:1, and both buprenorphine and naloxone (or their salts) being intended to be released within less than two minutes.

4.2 It was common ground that document D2 was a suitable starting point for assessing inventive step.

4.3 While envisaging dosage forms combining buprenorphine and naloxone in order to lower the risk of abuse, as also suggested in the patent in suit and claimed in auxiliary request IIa, document D2 does not indicate the ratio of these active agents (see D2: claim 8 and page 7).

4.4 Starting from the teaching of document D2, the following partial technical problems can be identified:

(i) to provide a specific fast-releasing oral mucosal dosage form of buprenorphine combined with naloxone;

(ii) to identify a suitable ratio of buprenorphine to naloxone.

4.5 The solution to the first partial problem would have been obvious to the person skilled in the art for the same reasons as set out above (see section 2) in the context of auxiliary request Ia, additionally taking into account that the combination of buprenorphine with naloxone was known (e.g. from D2), as also acknowledged in the patent in suit and the application as filed (see paragraph [0012] of the patent and the corresponding

passage on page 3, fourth paragraph of the application as filed, discussing Suboxone®).

4.6 A solution to the second partial problem was known, since a sublingual tablet with a 4:1 ratio of buprenorphine to naloxone was commercially available, as is clear from document G18 (Suboxone®, see page 1, lines 1 to 5; page 9, "Dosage and Administration"). The same ratio was used in earlier studies of that combination of active agents (see document D6: Abstract and page 6: "4. Discussion"). Verifying that a broader range of from 1:1 to 10:1 extrapolated around that ratio was practicable would have been routine work for the person skilled in the art.

4.7 As a consequence, the subject-matter of claim 1 of auxiliary request IIa does not involve an inventive step within the meaning of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated