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**Datasheet for the decision  
of 25 July 2017**

**Case Number:** T 0259/15 - 3.3.07

**Application Number:** 10185240.8

**Publication Number:** 2305194

**IPC:** A61F13/00, A61K31/485,  
A61K9/70, A61P25/04

**Language of the proceedings:** EN

**Title of invention:**

A buprenorphine transdermal patch for use in the treatment of pain for a dosing interval of at least 7 days

**Patent Proprietor:**

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Mundipharma Pharmaceuticals B.V.  
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**Opponents:**

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Murray, Adrian D'Coligny  
tesa Labtec GmbH

**Headword:**

Buprenorphine patch/EURO-CELTIQUE

**Relevant legal provisions:**

EPC Art. 56

**Keyword:**

Inventive step - (no)

**Decisions cited:**

T 1742/12, T 0293/07, T 0091/98, T 0847/07, T 1545/08



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Case Number: T 0259/15 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 25 July 2017**

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**Decision under appeal:**      **Decision of the Opposition Division of the European Patent Office posted on 22 December 2014 rejecting the opposition filed against European patent No. 2305194 pursuant to Article 101(2) EPC.**

**Composition of the Board:**

**Chairman**                      J. Riolo  
**Members:**                      A. Usuelli  
    C. Heath

## Summary of Facts and Submissions

- I. European patent No. 2 305 194, based on European patent application No. 10185240.8, was granted on the basis of 6 claims.

Independent claim 1 read as follows:

"1. A buprenorphine transdermal delivery device comprising a polymer matrix layer containing buprenorphine or a pharmaceutically acceptable salt thereof, for use in treating pain in humans for a dosing interval of at least 7 days, wherein the transdermal delivery device comprises 10 %-wt buprenorphine base, 10 to 15 %-wt levulinic acid, about 10 %-wt oleylolate, 55 to 70 %-wt polyacrylate and 0 to 10 %-wt polyvinylpyrrolidone".

Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed and of the parent and grandparent applications.

The following documents were among those cited during the opposition proceedings:

D1: WO 96/19975

D2: Journal of pharmaceutical sciences, 83, 2 (1994), pages 126-130

D5: US 5,240,711

D6: US 5,225,199

D8: US 5,026,556

D9: Therapeutische Systeme, 1984, 4th Edition, pages 26, 27 and 48-53

D11: US 4,956,171

- II. By decision posted on 22 December 2014, the opposition division rejected the oppositions.

Concerning the requirement of inventive step, the opposition division held that both document D1 and document D11, relating to transdermal devices for the administration of buprenorphine, represented reasonable starting points for the assessment of inventive step. These documents failed to disclose the use of the transdermal devices in the treatment of pain for a dosing interval of at least 7 days. The technical problem to be solved in the light of these documents was to be seen in the provision of convenient and effective pain treatment with buprenorphine from a transdermal delivery device. Some prior art documents indicated that for certain active agents, a dosing interval of 7 days was feasible. However, as explained in D9, a large amount of active ingredient was required. Furthermore, problems of skin irritation could limit the use of transdermal devices. Hence, the skilled person would have had no reasonable expectation of success when attempting to use the buprenorphine devices of D1 and D11 over a dosing interval of 7 days.

The requirement of Article 56 EPC was therefore met.

- III. The opponents (hereinafter: appellant-opponent I, appellant-opponent II and appellant-opponent III) lodged an appeal against that decision.
- IV. With their reply to the appeals dated 21 September 2015 the patent proprietors (hereinafter: the respondents) requested that the appeals be dismissed and submitted five auxiliary requests.

Auxiliary request 1 consisted of a single claim identical to claim 1 as granted.

Claim 1 of auxiliary requests 2 and 3 differed from claim 1 as granted in the deletion of the words "at least" before the feature "7 days".

Claim 1 of auxiliary requests 4 and 5 differed from claim 1 of auxiliary requests 2 and 3 in the deletion of the word "about" before the feature "10 %-wt oleyloleate".

- V. A request of intervention pursuant to Article 105 EPC, was submitted on 3 January 2017 by tesa Labotech GmbH (hereinafter: the intervener). In a communication dated 2 June 2017, the Board expressed its opinion that the intervention was admissible.
- VI. Oral proceedings were held on 25 July 2017. For information on the course of the oral proceedings, reference is made to the minutes.
- VII. The appellant-opponents and the intervener argued on inventive step starting from document D1 as the closest prior art. They considered that the subject-matter of claim 1 of the patent differed from the disclosure of D1 mainly in the indication that the transdermal delivery device was used for a dosing interval of at least 7 days. In their view, it was evident to a skilled person that using a transdermal device over a long dosing period was advantageous for patients in terms of comfort and convenience. The transdermal device disclosed in D1 was a promising candidate for a convenient method of treating pain with a buprenorphine patch. It would have been obvious therefore to carry out clinical tests with this device in order to



establish for how long it could be applied. This would have led the skilled person to the observation that the patch of D1 could effectively be used over a dosing period of at least 7 days as claimed in the patent. Such clinical tests were relatively simple and could be made with healthy persons. Considerations of reasonable expectation of success were not relevant in the present case since it was easy for the skilled person to carry out tests in order to verify whether the patch of D1 was suitable for a long dosing period. Thus, claim 1 of the patent was not inventive. The same considerations applied to the subject-matter of the auxiliary requests.

VIII. The respondents arguments on inventive step can be summarised as follows.

The main purpose of the invention underlying document D1 was to provide a better penetration enhancer. However, this document did not disclose any clinical data and did not provide any information about e.g. the dosing interval or the effective plasma concentration. In that respect, documents D2 or D11 were more appropriate starting points for the assessment of inventive step. Selecting document D1 as the closest prior art because it described the same patch as the patent in suit was based on hindsight.

The subject-matter of claim 1 was nonetheless inventive, even starting from document D1 as the closest prior art. The main distinguishing feature was the dosing interval of at least 7 days. The skilled person knew, for instance from D9, that the amount of active ingredient contained in a patch was much higher than the amount actually delivered to the patient. He was also aware that buprenorphine does not penetrates

human skin well, as reported in D5, and that it may cause irritation, as indicated in D6 and D8. Thus, when considering the possibility of using the patch of D1 over a dosing period of at least seven days, the skilled person would have very low expectations of success. There was no indication in this document to apply the patch on humans for such a long period. There was no way to calculate the absorption rate in humans from the data of D1, relating to experiments carried out using mouse skin. Thus, the skilled person would not have tested the device of D1. Furthermore, to determine the dosing interval of a patch, it was necessary to perform clinical tests. The case law of the boards of appeal clearly excluded a "try-and-see" approach to situations in which clinical tests were involved.

- IX. The appellants and the intervener requested that the decision under appeal be set aside and that the patent be revoked.
  
- X. The respondents requested that the appeal be dismissed, or alternatively that the patent be maintained on the basis of one of auxiliary requests 1 to 5 as filed with letter dated 21 September 2015.

## **Reasons for the Decision**

### MAIN REQUEST (PATENT AS GRANTED)

#### 1. Inventive step

The invention underlying the patent in suit relates to a transdermal delivery device for the administration of buprenorphine, an opioid analgesic agent.

1.1 Closest prior art

1.1.1 The Board agrees with the opposition division's conclusion that document D1 is the closest prior art. This document relates to transdermal devices for the administration of active ingredients. In particular, it addresses the problem of enhancing the absorption of the active ingredient through the skin (see page 1, third paragraph and page 2, fourth paragraph). Document D5, discussed in paragraph [0007] of the patent in suit, explains that one of the major problems with the transdermal administration of buprenorphine is that this substance only badly penetrates through the human skin (column 2, lines 32 to 34). This would have directed the skilled person to consider document D1. Moreover, the teaching of this document is focused on transdermal formulations of buprenorphine. Indeed, all the five examples of D1 concern devices containing this analgesic opioid as active ingredient. Lastly, the transdermal device of example 3 is the same device as that of the purpose-limited product claim 1 of the patent in suit.

1.1.2 Documents D2 and D11, proposed by the respondent as alternative closest prior-art documents, are in the Board's view less promising starting points for the assessment of inventive step.

D2, as pointed out by the respondent, provides more experimental data than D1 about the absorption of the active ingredient (see table 2 to 8). However, it is less instructive regarding the transdermal device used: there is only a general indication of the adhesive used ("amine resistance silicone") and the amounts in which buprenorphine and the excipients are included in the

device are not clear (see page 127 paragraph "Preparation of matrix device"). Moreover, D2 does not specifically address the problem of enhancing the penetration of buprenorphine.

Document D11 relates to drug delivery systems with increased drug permeability (column 2, lines 41 to 50). Example 3 describes a matrix-type transdermal delivery device comprising buprenorphine as active ingredient and discloses the *in vitro* flux of the active ingredient through human cadaver skin. The Board notes that whereas D1 describes the same buprenorphine device as that referred to in claim 1 of the patent in suit, example 11 concerns a different type of transdermal device. Thus, whilst both documents appear to be equally relevant when the purpose or the effect of the inventions is considered, D1 comes closer to the subject-matter of the patent in suit when the structure of the devices is considered.

In the respondent's view, the skilled person would attach more weight to D11 since it discloses data on the flux of the active ingredient, whereas D1 only provides data on the percentage of buprenorphine that penetrates mouse skin in an *in vitro* experiment. However, in the Board's view, the fact that D1 does not disclose data on the flux of the active ingredient would not lead the skilled person to disregard it. After all, D1 specifically addresses the problem of providing transdermal buprenorphine devices with increased absorption. Moreover, the fact that in 1992, when document D5 was filed, the poor penetration of buprenorphine was still regarded as a major problem (see point 1.1.1 above) could have led the skilled person to conclude that the devices of D11, described in 1989, were unsatisfactory. In this respect he would

have possibly regarded the device described in document D1, which was filed more than six years after D11, as more promising.

1.1.3 In any case the Board notes that according to the established case law of the boards of appeal, when two or more prior-art documents could reasonably be used as the starting point for the assessment of inventive step, a conclusion that the subject-matter claimed is inventive can only be reached after assessing this requirement starting from all the possible closest prior art (see for instance T 1742/12, reasons 5 to 6.6). Hence, in the present case, the respondent cannot argue against assessing inventive step starting from D1 as the closest prior art as well.

1.1.4 As mentioned above, the transdermal device of example 3 of D1 has the same features as the device of claim 1 of the patent in suit. This device was tested in an *in vitro* experiment in which it was applied to mouse skin for 24 hours. Document D1 fails to disclose the use of the transdermal device of example 3 in humans for a dosing interval of at least 7 days.

1.2 Technical problem

1.2.1 The opposition division defined the technical problem as the provision of convenient and effective pain treatment with buprenorphine from a transdermal delivery device. The Board agrees with this formulation of the technical problem. The "convenience" of the treatment is due to the possibility of using the transdermal device for a dosing interval of at least 7 days.

1.3 Obviousness

1.3.1 The skilled person approaching the problem of providing a method of pain treatment based on the use of a buprenorphine-containing transdermal device would have regarded the patch of example 3 of D1 as a promising candidate to be tested in experimental trials. Indeed, as explained above, the poor penetration of buprenorphine through human skin constituted a major hurdle in the development of methods of pain treatment using a buprenorphine patch. Document D1, however, addresses this problem and discloses in example 3 a device that in an *in vitro* test provides the best results in terms of the percentage of buprenorphine that penetrates mouse skin. Although the skilled person would have been aware that positive results obtained in experimental models are not necessarily confirmed in clinical tests, the Board sees no reason why he should have been sceptical about the possibility of using the device of example 3 of D1 effectively on humans. On a fair reading, it is apparent that the purpose of D1 is to provide useful transdermal devices for the treatment of pain in humans.

1.3.2 Also the concern about any possible problem of skin irritation caused by the use of the patch of D1 would not have discouraged the skilled person from testing it. After all, the experiments described in D6 (examples 5 and 11) indicate that the applying a buprenorphine patch to the shaved back of rats does not cause any skin rash. In line with these results, D8 describes compositions for the transdermal delivery of buprenorphine that do not cause major problems of skin irritation (column 3, lines 5 to 11). Moreover, any possible problem of skin irritation in a patient during

a clinical test could possibly be handled by discontinuing the application of the patch.

Hence, the skilled person would not have considered the potential problems of skin irritation as a major hurdle.

- 1.3.3 Thus, in the Board's view, the skilled person would have been encouraged to test the device of example 3 of D1 on human subjects. Furthermore, considering that the therapeutic application of buprenorphine (pain treatment) was well known, the main objective of these tests would have been to determine whether the active ingredient does indeed penetrate through human skin and for which dosing interval the device can be used. Concerning this second aspect, the Board agrees with the respondents that for reasons of comfort and convenience a user would normally prefer transdermal devices that can be applied to the skin over longer periods. Thus, a skilled person would be obviously interested in determining the maximum duration of effective application of a transdermal device.

Valuable data in relation to the above objectives could be obtained by applying the patch to human subjects and monitoring the levels of buprenorphine in the plasma, bearing in mind that the minimal effective concentration is 100 pg/ml (paragraph [0128]). This is what has been done in the test described in example 1 of the patent.

The data reported in Table 1 indicate that the level of 100 pg/ml is reached between 36 and 42 hours after patch application. Thereafter, the buprenorphine concentration remains above 100 pg/ml until the end of the seventh day. In the Board's view the observation

that the levels of buprenorphine in the plasma were still above the minimum effective concentration for the treatment of pain after e.g. 2, 3 or 4 days would have encouraged the skilled person to test the patch over longer periods.

Thus, in the Board's opinion, the skilled person would have observed that the device of example 3 of D1 could be used for a dosing interval of at least 7 days by performing tests which simply require applying the patch of D1 and monitoring the level of buprenorphine in the blood.

- 1.3.4 In line with the appealed decision, the main argument of the respondent in support of the presence of inventive step was that the skilled person would not have started such clinical tests in the absence of a reasonable expectation of success.

The Board concurs with the respondent that on the basis of the experimental data disclosed in D1 it would not have been possible to predict whether the device of example 3 could be used to treat pain in humans for a dosing period of at least seven days. Indeed, D1 does not provide any data on the penetration of the active ingredient through human skin. Furthermore, as explained for instance in D9 (page 51, third paragraph), the amount of active ingredient contained in a transdermal device is usually higher than the amount actually released. The excess amount depends *inter alia* on the type of active ingredient, and the prior art does not provide any clear data in relation to buprenorphine. Thus, the skilled person would not have been able to estimate the maximum dosing interval of the device of example 3 on the basis of the amount of buprenorphine it contained.



Despite this, the Board considers that the skilled person would have had no reason to be pessimistic and therefore to abandon the idea of testing a promising device.

- 1.3.5 According to the established case law of the boards of appeal, the general idea behind the concept of "reasonable expectation of success", which has been developed in particular in the field of biotechnology, is that in certain circumstances the person skilled in the art, on the basis of his common general knowledge or the teaching of the prior art, may be able to theoretically conceive a straightforward approach to solve a given technical problem. However, the practical implementation of that approach and/or the experimentation required to verify whether it does indeed work, may involve, for instance, overcoming technical difficulties (Case Law of the Boards of Appeal of the EPO, 8th edition (2016), I.D.7.1). In such circumstances, the skilled person would possibly avoid embarking on a troublesome experimentation if he did not have a reasonable expectation of success. On that basis, inventive step may be acknowledged even if the prior art contains a teaching to follow that approach.

However, the concept of "reasonable expectation of success" does not apply when the implementation and the testing of an approach suggested by the prior art do not involve any particular technical difficulties (see T 293/07 point 36 of the Reasons and T 91/98 point 8 of the Reasons). In such situations the skilled person would prefer to verify whether the potential solution that he has conceived works, rather than abandon the project because success is not certain.

The Board holds that this is the situation in the present case.

- 1.3.6 For the reasons explained above, the skilled person would regard the patch disclosed in example 3 of D1 as a potentially suitable candidate for solving the technical problem. He would furthermore consider that verifying the effectiveness of this potential solution would be unlikely to require particularly challenging experiments.

Indeed, buprenorphine is a well-known active ingredient used clinically for the relief of acute and chronic pain (D2, first paragraph). The minimum effective concentration for providing analgesia was known before the priority date of the patent (D2, page 139, right column). A preliminary assessment of the possibility of using the transdermal device of D1 for effective and convenient treatment of pain can be made by applying the device to volunteers and observing whether and for how long the plasma concentration of buprenorphine is above the minimum threshold. This is in the essence the experiment described in paragraphs [0103] and [0104] of the patent. In this context the Board notes that before the priority date of the patent buprenorphine was already administered by various routes, including intravenously (D2, page 126, right column, lines 1 to 5). This mode of administration provides peaks of plasma concentration which are much higher than those obtained with transdermal administration (see also Table 8 of the patent). Since the severity of the side effects of a drug is generally proportional to its plasma concentration, the skilled person evaluating the possibility of testing the patch of D1 on humans was in a position to make a realistic assessment of the

potential risks for the volunteers. Furthermore, the tests can be carried out with healthy human subjects to reduce the dangers of potential side effects. It is also emphasised that in the present context the Board is not being asked to assess the difficulties involved in carrying out all the clinical trials required to obtain a pharmaceutical authorisation. Here the point is whether the skilled person would start the tests necessary to determine the maximum length of use of the patch of D1. For the reasons described above, the Board considers that these studies are based on routine experiments and do not involve a high level of risk to the health of the subjects.

- 1.3.7 The respondent has argued that a skilled person would not conduct tests on human subjects in the form of a try-and-see screening approach if he did not have a reasonable expectation of success.

In the Board's opinion this issue cannot be approached in abstract terms but it needs to be considered in relation to the circumstances of each specific case. It is agreed that trials involving experimentation in humans demand, in general terms, a cautious approach. Nevertheless, the technical difficulties involved in such experiments, the risks to the subjects and the ethical concerns are highly variable. In the present case, the experimentation required to verify whether the patch of D1 can be used effectively for convenient pain therapy is relatively simple and does not involve major risks for the volunteers. Furthermore, no relevant argument has been submitted regarding any possible ethical issue.

Thus, in the circumstances of the present case, the Board considers that the skilled person would test the

device of D1 on human subjects despite the uncertainties as to the maximum duration of application.

- 1.3.8 The Board is aware of decisions T 293/07, T 847/07 and T 1545/08 in which a "try-and-see" approach was denied in circumstances in which experiments on human beings were involved.

The invention underlying case T 293/07 related to the use of erythropoietin (Epo) for producing a peripherally applied pharmaceutical for the treatment of stroke in humans. The deciding board came to the conclusion that the skilled person would not have adopted a "try-and-see" approach to verify whether Epo could indeed be used for the treatment of stroke. However, a key aspect of the Board's reasoning was the consideration that carrying out a study on humans, with the objective of developing therapeutic measures for the treatment of stroke, could not be regarded as a well-established routine activity. In addition, it was highly doubtful whether Epo could cross a compromised blood-brain barrier (see point 37 of the Reasons). The present case differs from that of decision T 293/07 at least because the effectiveness of the solution suggested in the prior art (i.e. the patch of D1), can be tested through routine experimentation.

In T 847/07, the Board held that it was "questionable whether the skilled person would adopt a "try and see" attitude at all in cases such as the present one where extensive in vivo animal and ultimately human testing would be necessary in order to determine whether or not a compound has a certain property." The case concerned formulations comprising highly purified recombinant coagulation factor VIII. The decision did not discuss

which *in vivo* testing would have been required for determining the property of factor VIII. The Board notes that the present case concerns a clinically used active ingredient with therapeutic properties that are already known. The patch defined in claim 1 of the patent in suit is the same patch as that described in D1. For the reasons explained above, the Board considers that assessing whether this patch can solve the problem defined in point 1.2.1 above does not involve extensive testing on animals and humans.

In decision T 1545/07 the Board concluded that the skilled person was not in a "try-and-see" situation by referring to the principles discussed in T 293/07 and T 847/07 (see points 93 and 94 of the Reasons).

In the Board's view, the case law does not support the conclusion that the skilled person would systematically avoid a "try-and-see" approach whenever testing on human patients is involved, regardless of the specific circumstances of the case.

- 1.4 For the above reasons, the Board concludes that the subject-matter of claim 1 of the patent does not meet the requirements of Article 56 EPC.

#### AUXILIARY REQUESTS 1 to 5

2. The amendments made in the auxiliary requests (see point IV above) do not alter the above assessment of inventive step regarding the subject-matter of the main request. Indeed, the parties did not submit any inventive step arguments specific to the auxiliary requests. Therefore, the Board concludes that auxiliary requests 1 to 5 do not meet the requirements of Article 56 EPC.

**Order**

**For these reasons it is decided that:**

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated