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Datasheet for the decision of 17 June 2022

Case Number: T 1279/21 - 3.3.07

Application Number: 08839155.2

Publication Number: 2207507

IPC: A61K9/70, A61K31/4468

Language of the proceedings: EN

Title of invention:
ONCE-A-DAY REPLACEMENT TRANSDERMAL ADMINISTRATION OF FENTANYL

Patent Proprietor:
Alza Corporation

Opponent:
Hexal AG

Headword:
Once-a-day replacement transdermal administration of fentanyl / ALZA

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

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Case Number: T 1279/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 17 June 2022

Appellant: (Opponent)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)
Respondent: (Patent Proprietor)	Alza Corporation 700 Eubanks Drive Vacaville, CA 95688 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 11 June 2021 concerning maintenance of the European Patent No. 2207507 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. European patent 2 207 507 (the patent) was granted on the basis of 18 claims.

Claim 1 of the patent read as follows:
"A kit for administering a drug with a transdermal patch, comprising:
(a) a transdermal patch for administration of fentanyl base through the skin, comprising:
a backing layer;
a reservoir disposed on the backing layer, at least the skin contacting surface of the reservoir being adhesive;
the reservoir comprising a polymeric composition containing polyacrylate and an amount of fentanyl base sufficient to induce and maintain analgesia in a human for one day; and
(b) an instruction print including instruction on daily replacement of the transdermal patch,
wherein the normalized area based on nominal dose strength is 0.2 to 0.4cm^2 per µg/h per day and the fentanyl base loading per surface is 0.14 to 0.3 mg/cm^2."

Claim 8 read as follows:
"A transdermal patch for administering of fentanyl base through the skin, comprising:
a backing layer;
a reservoir disposed on the backing layer, at least the skin contacting surface of the reservoir being adhesive;
the reservoir comprising a polymeric composition containing polyacrylate and an amount of fetanyl

[*sic*] base sufficient to induce and maintain analgesia in a human for one day,
wherein the normalized area based on nominal dose strength is 0.2 to 0.4cm^2 per µg/h per day and the fentanyl base loading per surface area is 0.14 to 0.3 mg/cm^2"

Claim 9 read as follows:
"Fentanyl base for use in a method of treating pain, the method comprising replacing one monolithic transdermal patch daily on the skin of a human in need thereof, wherein the patch contains a backing and a reservoir comprising a polymeric composition containing polyacrylate and fentanyl base, wherein the normalized area based on nominal dose strength is 0.2 to 0.4cm^2 per µg/h per day and the fentanyl base loading per surface area is 0.14 to 0.3 mg/cm^2."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked an inventive step, it was not sufficiently disclosed and it extended beyond the content of the application as filed.

III. The appeal opposition division took the interlocutory decision that, on the basis of the auxiliary request MR-A' filed on 11 January 2021, the patent met the requirements of the EPC.

The decision was based on the patent as granted as the main request, and on auxiliary request MR-A'. Auxiliary request MR-A' only differed from the patent as granted by the deletion of claim 18.

IV. The decision cited in particular the following documents:

D3: US 5 186 939 A
D4: US 2005/208117 A1

V. Regarding inventive step for auxiliary request MR-A', the opposition division decided the following:

The closest prior art D3 disclosed a patch for administering fentanyl trans-dermally comprising a backing layer and an adhesive fentanyl reservoir layer containing polydimethylsiloxane. The only significant differentiating feature was the presence of an acrylate polymer instead of a polydimethylsiloxane. The technical effect linked to this difference was a higher solubility of fentanyl in the acrylate polymer. The objective technical problem was the provision of an alternative analgesic patch containing fentanyl for daily replacement with a low amount of residual opioid. The claimed solution involved an inventive step in light of D3 and D4.

VI. The opponent (appellant) lodged an appeal against the interlocutory decision of the opposition division.

VII. The appeal was notified to the patent proprietor (respondent) by letter dated 12 August 2021. The statement of grounds of appeal of the appellant was notified to the patent proprietor by letter dated 25 October 2021. No reply was received.

VIII. The appellant's arguments regarding inventive step may be summarised as follows:

D3 represented the closest prior art. D3 disclosed a patch for administering fentanyl transdermally, comprising a backing layer and an adhesive fentanyl reservoir layer comprising polydimethylsiloxane. The

patch was for once-daily administration. The only significant difference between the transdermal therapeutic systems of document D3 and the claimed subject-matter was the presence of an acrylate polymer.

No comparative data over the disclosure of document D3 had been produced. Additionally, the claimed analgesic patches did not achieve a low amount of residual opioid. Accordingly, the problem to be solved was the provision of alternative patches to the patches of document D3, wherein it was accepted that the residual amount of opioid was significantly higher than in the patches of document D3.

The skilled person knew from D4 that fentanyl could be administered *via* transdermal therapeutic systems on the basis of polyacrylate, and that subsaturated polyacrylate patches could provide an analgesic effect for three or more days, and thus also for one day. Accordingly, the criteria of inventive step were not met.

IX. The appellant requests that the decision under appeal be set aside and that the patent be revoked.

Reasons for the Decision

1. Basis for the decision

The present decision is based on the request allowed by the opposition division, namely auxiliary request MR-A'. The respondent did not submit any other request in appeal proceedings, nor filed any reply to the statement of grounds of appeal.

2. Inventive step

2.1 The invention pertains to transdermal patches and kits for transdermal delivery of fentanyl base. The purpose of the invention is to provide a patch for daily replacement (once-a-day patch, or 1-day patch) for transdermal delivery of fentanyl base at a targeted rate and in an amount sufficient to induce and maintain analgesia over a period of treatment that lasts about one day (see paragraph [0006]).

2.2 D3 also relates to transdermal fentanyl patches for once daily administration. The patches of D3 comprise, among others (see column 2):
(a) a backing layer,
(b) an adhesive fentanyl reservoir layer that comprises in particular 1-5 wt% fentanyl base and 85-98 wt% of an amine resistant, pressure sensitive adhesive polymer (such as polydimethylsiloxane, see claim 4).

2.3 The opposition division decided that the features of claim 1 relating to the normalized area based on nominal dose strength of 0.2-0.4cm^2 per µg/h per day did not establish a difference over D3, nor did the features pertaining to the fentanyl base loading per surface area of 0.14-0.3 mg/cm^2. This has not been contested in appeal.

2.3.1 Thus, the fentanyl loading per surface in D3 (see column 3, lines 48-52) is 0.15-0.5 mg/cm^2, preferably 0.17-0.3 mg/cm^2, which is encompassed by the range of 0.14 to 0.3 mg/cm^2 of claim 1.

2.3.2 Furthermore, as calculated by the opposition division, the preferred steady state flux of 2-10 µg/cm^2/hr over the first one day of use shown in D3 (see column 4,

lines 31-35) leads to a the normalized area based on nominal dose strength of 0.1-0.5 cm^2 per µg/hr, with a calculated value of 0.13 cm^2 per µg/hr in example 2 of D3. The claimed range of 0.2 to 0.4 cm^2 per µg/h per day is therefore not seen as a novel selection.

2.4 The subject-matter of claim 1, 8 or 9 thus only differs from the patches of D3 in that the polymeric composition contains polyacrylate.

2.5 No comparable data was adduced to demonstrate that any effect over D3 is associated with this differentiating feature.

In this respect, the Board concurs with the appellant that an effect of having a low amount of residual opioid cannot be taken into account for the formulation of the technical problem. Such an effect is neither a feature of the claims nor is it shown to arise as a result of the differentiating feature. In D3 (see examples 1 and 2), the amount of residual opioid after 24 hours is 15% (i.e. 85% delivery), whereas in example 5 of the patent, the amount of residual opioid for the 1-day patches QD 38 µm and QD 25 µm is at least 57% (i.e. respectively 29% and 43% delivered).

2.6 Consequently, the problem to be solved is to provide an alternative analgesic patch containing fentanyl for daily replacement.

2.7 The question is thus whether the skilled person would consider the use of a polyacrylate in the matrix in order to solve the above problem.

2.7.1 D4 discloses a transdermal patch for administering fentanyl base through the skin over an extended period

of time, such as at least 3 days. The patch of D4 comprises (a) a backing layer; (b) a reservoir disposed on the backing layer, at least the skin contacting surface of said reservoir being adhesive; said reservoir comprising a single phase polymeric composition (comprising acrylate polymer), free of undissolved components containing an amount of fentanyl or an analog thereof sufficient to induce and maintain analgesia in a human for at least three days. Thus the skilled person knows from D4 that polyacrylate polymers may be employed as adhesive matrix in fentanyl patches.

As calculated in the decision (see paragraph 14.8.2), the normalized area based on nominal dose strength in D4 is e.g. from 0.33 to 0.5 cm^2 per µg/h (see the even more preferred steady state drug flux of about 2 to about 3 $\mu g/cm^2/hr$ in paragraph [67]), and the fentanyl loading per surface may be from about 0.12 mg/cm^2 to about 0.5 mg/cm^2 of fentanyl (see paragraph [53]), e.g. 0,35 mg/cm^2 in example 4. Accordingly, the polyacrylate-based patch of D4 allows for values for the normalized area based on nominal dose strength and fentanyl loading per surface which largely overlap those of D3 and of claim 1.

2.7.2 The decision nonetheless concludes that the claimed subject-matter involves an inventive step over D3 and D4. The opposition division reasoned that D3 related to a depot patch for daily replacement, containing fentanyl in a concentration above saturation in a polymer matrix (polydimethylsiloxane) with poor solvent properties, thus permitting a rapid release of fentanyl over about 1 day with a low amount of residual opioid thereafter. In contrast, D4 pertained to a subsaturated patch allowing delivery of fentanyl over at least 3 days, using a polymer matrix (polyacrylate) with a

higher solubility for the drug. The opposition division concluded that the skilled person would not consider to replace the polydimethylsiloxane of D3 by the acrylate polymer of D4, because a depot patch did not have the same pharmacokinetics as a subsaturated patch, and because D4 still contains a substantial amount of fentanyl after 24 h of usage.

However, the objective technical problem is only the provision of an alternative analgesic patch containing fentanyl for daily replacement. The skilled person does not seek to avoid high residual amounts of fentanyl in the patch after 24 h of usage. On the contrary, as shown above (see 2.5), the 1-day patches according to the invention may leave 57% or more residual opioid. It is furthermore shown in D4 that polyacrylate-based patches can induce and maintain analgesia in a human for at least three days, and hence can also provide an analgesic effect for one day. Thus the skilled person, looking for an alternative to the transdermal therapeutic system of D3, and accepting a higher residual amount of fentanyl, would consider the use of polyacrylate as in D4 as an obvious solution.

Accordingly, the criteria of inventive step are not met.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated