Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 9 September 2024

Case Number: T 0783/22 - 3.3.07

Application Number: 12840025.6

Publication Number: 2767285

IPC: A61K9/20, A61K9/28, A61K31/496, A61K47/02, A61K47/10, A61K47/12, A61K47/26, A61K47/38

Language of the proceedings: EN

Title of invention:
TABLET COMPRISING 7-[4-(4-BENZO[b]THIOPHEN-4-YL-PIPERAZIN-1-YL) BUTOXY]-1H-QUINOLIN-2-ONE OR A SALT THEREOF

Patent Proprietor:
Otsuka Pharmaceutical Co., Ltd.

Opponents:
Maiwald GmbH
Teva Pharmaceutical Industries Ltd.

Headword:
Brexpiprazole tablet / OTSUKA

Relevant legal provisions:
RPBA 2020 Art. 12(4), 12(6)
EPC Art. 56

Keyword:

Late-filed document - admitted (no)
Inventive step - (yes)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0783/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 9 September 2024

Appellant: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. Tel Aviv 6944020 (IL)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Otsuka Pharmaceutical Co., Ltd. 9, Kanda-Tsukasamachi 2-chome Chiyoda-ku Tokyo 101-8535 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Party as of right: (Opponent 1)	Maiwald GmbH Postfach 33 05 23 80065 München (DE)
Representative:	Maiwald GmbH Elisenhof Elisenstraße 3 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 31 January 2022 concerning maintenance of the European Patent No. 2767285 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	S. Ruhwinkel

Summary of Facts and Submissions

I. The appeal was filed by opponent 2 (appellant) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed on 25 January 2021, the patent met the requirements of the EPC.

II. Claim 1 of the main request pertained to:

"A tablet comprising 7-[4-(4-benzo[b]thiophen-4-yl-piperazin-l-yl)butoxy]-1H-quinolin-2-one or a salt thereof as an active ingredient, an excipient (a), a binder (b), a disintegrant (c) and a lubricant (d),
wherein the excipient (a) is at least one member selected from the group consisting of lactose, corn starch, and microcrystalline cellulose;
the binder (b) is hydroxypropyl cellulose;
the disintegrant (c) is at least one member selected from the group consisting of low-substituted hydroxypropyl cellulose, croscarmellose sodium, and sodium carboxymethyl starch; and
the lubricant (d) is magnesium stearate;
the tablet further comprising a coating layer on the surface thereof,
wherein said coating layer comprises a colorant (e), and the colorant (e) comprises iron oxide."

In the following, the active ingredient 7-[4-(4-benzo[b]thiophen-4-yl-piperazin-l-yl)butoxy]-1H-quinolin-2-one is referred to by its international non proprietary name brexpiprazole.

III. The following documents were cited in the appealed decision:

D1: US 2011/152286
D6: Handbook of Pharmaceutical Excipients, Sixth Edition, Eds. R.C. Rowe et al., Pharmaceutical Press, London, 2009
D14: Pharmaceutical Dosage Forms: Tablets, Third Edition, Volume 2: Rational Design and Formulation, Eds. L.L. Augsburger and S.W. Hoag, Informa Healthcare, New York and London, 2008, pages 269-292
D15: Physicians' Desk Reference®, entry "Ability®" (page 882), 61st edition, 2007
D17: EP 2 359 816 A1
D20: WO 2006/097344 A1
D21: Pharmaceutical Preformulation and Formulation, Second Edition, Ed. M Gibson, Informa Healthcare, New York and London, 2009, chapter 3, pages 81-86

IV. With respect to inventive step, the opposition division selected D1 as closest prior art document. The claimed subject-matter differed from the tablet disclosed in D1 by the binder, the disintegrant, and the coating comprising iron oxide. The opposition division applied the partial problem approach, and, in relation to the presence of iron oxide in the coating, formulated the partial problem as the provision of a tablet formulation for brexpiprazole with improved photostability. None of D6, D14, D17 or D20 led to the claimed solution. In addition, not only the claimed solution but also the discovery of a new problem, namely the photosensitivity of brexpiprazole, rendered the claimed subject-matter inventive.

V. With their grounds of appeal, the appellant submitted the following document:

D24: EMA Assessment report for Rxulti® (brexpiprazole), EMA/556923/2018, 31 May 2018

VI. The Board set out their preliminary opinion in a communication under Article 15(1) RPBA.

VII. Oral proceedings were held before the Board in the presence of the appellant and of the patent proprietor (respondent).

VIII. The parties' requests were the following

(a) The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

(b) The respondent requested that the appeal be dismissed, so that the patent is maintained based on the main request filed 25 January 2021, or, alternatively, that the patent be maintained on the basis of the auxiliary request filed 25 January 2021. The respondent further requested that D24 be not admitted into the proceedings.

(c) Opponent 1, who is party as of right in the appeal proceedings, did not make any submission or request.

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

(a) D24 was filed in reaction to developments in the first instance proceedings, namely the change in the opposition division's position regarding the

improvement in photostability linked to the iron oxide-containing coating and the problem-invention concept. D24 explained that the photostability of brexpiprazole was not a real technical problem at the priority date of the patent. Hence D24 was to be admitted into the proceedings.

(b) Starting from D1 as the closest prior art, the differentiating features were the binder (b), the disintegrant (c), and that the coating (e) comprising iron oxide. Table 8 of the patent provided some indication of an improvement in photostability related to the iron oxide in the coating. However, considering the high level of illuminance and light intensity used, the data did not credibly show genuine photoinstability. The (partial) technical problem regarding the presence of iron oxide was the provision of a brexpiprazole tablet with improved photostability. The claimed solution did not involve an inventive step, firstly because iron oxide was a common colorant used to color tablets so as to facilitate their identification, and secondly because any of the known pigments would have solved the objective technical problem. Providing a rank order between these pigments based on their known property did not render the approach inventive. Hence the criteria of inventive step were not met.

X. The respondent's arguments may be summarised as follows:

(a) The limitation regarding the present of iron oxide in the coating was introduced already with the reply to the opposition. D24 was thus late filed. Furthermore, the statements in D24 regarding the

photostability of brexpiprazole as a bulk substance, or of the RXULTI tablets, were not *prima facie* relevant. D24 was not to be admitted into the appeal proceedings.

(b) Starting from document D1, the differentiating features were the active ingredient (brexpiprazole), the binder (b), the disintegrant (c) and the iron oxide (e) in the coating. The effect of the iron oxide-containing coating was an improved photostability. The conditions of illuminance and intensity used in table 8 were in this respect not excessive. The problem was to provide a brexpiprazole tablet with improved photostability. The claimed solution was based on the realization that brexpiprazole in pharmaceutical formulations gave rise to photostability problems. This problem was not known at the priority date. The argument that the addition of a colorant would have been obvious ignored the effect of improved photostability which was part of the technical problem. The particular selection of iron oxide was purposeful in view of its better results. Hence the criteria of inventive step were met.

Reasons for the Decision

1. Admittance of D24

1.1 The appellant submitted D24 with their grounds of appeal.

D24 represents an amendment to the appellant's case in the sense of Article 12(4) RPBA and its admission is subject to the Board discretion. According to Article 12(4) RPBA, the Board shall exercise its discretion in view of, *inter alia*, the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal, and the need for procedural economy.

In addition, under Article 12(6) RPBA, the Board shall not admit evidence which should have been submitted in the first instance proceedings, unless the circumstances of the appeal case justify their admittance.

1.2 The late filing of D24 in appeal proceedings is not justified by developments in the first instance proceedings, for the following reasons.

Already with the reply to the opposition, the respondent had not only filed the present main request, comprising the feature that iron oxide be present in the coating, but also argued in the context of inventive step starting from D1 that this iron oxide-containing coating improved light stability, and that "it was unknown at the priority date that brexpiprazole is prone to photodegradation" (see page 8 of the reply dated 25 January 2021). The appellant had ample time to address this feature and argumentation after the respondent's reply until the oral proceedings before the opposition division.

The appellant emphasizes that the opposition division changed their position regarding the improvement in photostability linked to the iron oxide-containing coating, i.e. dismissed the effect as not demonstrated

in their preliminary opinion dated 6 May 2021 (see §1.6.3), yet acknowledged it in the appealed decision (see §7.3.3). This change in position is however not decisive, considering that the appellant anyway agreed that this effect occurred (see §18 of their letter dated 4 October 2021). In any case, the opposition division's preliminary opinion more generally left open not only the assessment of inventive step but also the argument of problem-invention relating to brexpiprazole photodegradation. The appellant could therefore not assume that this aspect would not be found relevant by the opposition division. Under these circumstances, there is no justification for the appellant's submission of D24 at appeal stage only. The appellant should have made their case against the iron oxide-containing coating feature in the first instance proceedings in reply to the respondent's limitation of their main request using this feature, and was not exonerated by the open, preliminary opinion of the opposition division.

1.3 In appeal, the appellant relies on D24 as post-published evidence that the photostability of brexpiprazole was not a real technical problem at the priority date of the patent. D24 reports that the active substance brexpiprazole (i.e. not formulated) was assessed for photostability following the ICH guideline Q1B and was found to be not light sensitive (see §2.2.2, "Stability" on page 16). D24 further indicates that also the finished products, i.e. the Rxulti tablets for each strength, thus including the white, iron oxide-free 4 mg tablets, were tested for photostability and were not sensitive to light (see §2.2.1 on page 15; §2.2.3, "Description of the product and Pharmaceutical development" on page 17 and "Stability of the product" on page 18).

However, the appellant never contested, during the first-instance proceedings, that brexpiprazole (formulated or not) is photosensitive. The filing of D24 accordingly leads to the introduction of previously undebated issues. These submissions should have been made in the first instance proceedings (Article 12(6) RPBA).

1.4 Lastly, in the Board's view, the conclusion expressed in D24 that brexpiprazole (even formulated without iron oxide) is not photosensitive does not necessarily mean that no improvement is conceivable in this respect, or invalidate any data in the patent showing that such an improvement is achieved using iron oxide (see 2.4 below). In this sense, the Board does not consider D24 to be *prima facie* relevant, i.e. D24 does not suitably address the photostability issue which led to the appealed decision (Article 12(4) RPBA).

1.5 Consequently, the Board did not admit D24 into the appeal proceedings.

2. Main request, inventive step

2.1 The patent relates to tablets comprising brexpiprazole (also referred to as compound (I) in the patent), a compound known for the treatment of central nervous system diseases such as schizophrenia (see paragraphs [0002] and [0004] of the patent).

Claim 1 of the main request relates to a tablet comprising:
- brexpiprazole or a salt thereof as an active ingredient,

- an excipient (a) selected from lactose, corn starch, and microcrystalline cellulose,
- a binder (b) which is hydroxypropyl cellulose,
- a disintegrant (c) selected from low-substituted hydroxypropyl cellulose, croscarmellose sodium, and sodium carboxymethyl starch, and
- a lubricant (d) which is magnesium stearate,
- the tablet further comprising a coating layer on the surface thereof, wherein said coating layer comprises a colorant (e), and the colorant (e) comprises iron oxide.

2.2 The closest prior art D1 describes compounds for the treatment of central nervous system diseases such as schizophrenia (see paragraph [0043]). Brexpiprazole is listed as one of the preferred compounds in D1 (see paragraph [0029] and example 1 on page 16). D1 further discloses formulations comprising these compounds, such as tablets (see paragraph [0115]). The sole formulation example of D1 (see the preparation example on page 46) shows a tablet comprising a compound of the invention of D1 (in general terms), microcrystalline cellulose (Avicel) and corn starch (both corresponding to excipient (a)), magnesium stearate (i.e. lubricant (d)), and a coating composed of hydroxypropyl methylcellulose, PEG 6000, castor oil and ethanol.

2.3 The parties agree that the binder (b), the disintegrant (c), and the presence of iron oxide in coating (e) each represent a differentiating feature over D1.

Contrary to the respondent's view, the selection of brexpiprazole does not represent an additional difference. The preparation example on page 46 of D1 generally refers to "a compound of the present invention", which expresses that it is generally

applicable to the compounds disclosed therein. The single selection, in this formulation example, of brexpiprazole from the list of preferred compounds of D1 does not represent a differentiating feature. The preparation example of page 46 is the sole specific formulation example of D1 and cannot be regarded as a further selection. The fact that this preparation example does not indicate the unit dose and the weight of the tablet does not change this conclusion because these features are not required in claim 1 of the main request.

2.4 Technical effect of the differentiating features

The Board shares the opposition division's opinion that the binder (b) and disintegrant (c) are not convincingly shown to result in any particular technical effect. Tables 2 and 4 of the patent do not establish any effect associated with the particular components (b) and (c) of claim 1.

Hence the present case revolves around the differentiating feature pertaining to the presence of iron oxide in coating (e) and its technical effect on photostability.

The technical effect of the presence of iron oxide in coating (e) on improved photostability is shown by the forced degradation study presented in examples 3-1 to 3-9 and tables 7 and 8 of the patent:
- 3-1: uncoated tablets,
- 3-2, 3-3: tablets with a coating comprising titanium oxide,
- 3-3 to 3-7: tablets with a coating comprising titanium oxide and red or yellow ferric oxide,

- 3-8 and 3-9: tablets with a coating comprising titanium oxide and food blue #2 aluminium lake.

Upon exposure to light irradiation, a lower increase in impurity is observed in the claimed tablets in comparison not only with the uncoated tablets but also in comparison with the tablets with a coating containing only titanium oxide, or titanium oxide and aluminium lake (see 3-4 and 3-6 vs 3-2 or 3-8; 3-5 and 3-7 vs 3-3 or 3-9).

The appellant contends that the data do not credibly show genuine photoinstability, and criticises the high level of light exposure used to distinguish between the above pigments. In other words, the appellant accepts the existence of the effect, but contests its extent and its practical relevance. The Board does not share this view.

The conditions used in table 8:

> "visible light: total illuminance of 1.8 x 10^6 lux.hr; ultraviolet light: total intensity of 300 W.hr/m^2" (see paragraph [0075] of the patent)

are entirely consistent with the ICH recommendations for confirmatory studies described in D21:

> "photostability testing should consist of forced degradation and confirmatory testing. [...] Confirmatory studies involve exposing the compound to light whose total output is *not less* than 1.2 million lux hours and has a near-UV energy of *not less* than 200 W hr/m^2" (see the paragraph bridging pages 82 and 83, emphasis added by the Board).

The appellant did not show why the 50% increase in light exposure in the patent compared to the *lower* limits of D21 should make the observed differences in the pigments' photoprotective behaviours irrelevant for

the intended use and shelf-life of the tablets. The appellant's argument that there is very little difference between the behaviours of the pigments is thus merely subjective, and the allegation that no difference would be apparent using the minimal levels of illumination allowed by the ICH recommandations is speculative.

The appellant also relied on the fact that the white (iron oxide-free) tablets are commercially viable products. However, the fact that the tablet may be found satisfactory in the absence of iron oxide does not mean that an improvement in photostability cannot represent a tangible benefit in terms of the viability of the product.

2.5 Technical problem

Considering the effect associated with the presence of iron oxide in the coating, the technical problem is the provision of a brexpiprazole tablet with improved photostability.

2.6 Obviousness

2.6.1 The appellant firstly submits that iron oxide is a common colorant used to color tablets so as to facilitate their identification and distinguish between e.g. dosage strengths (see D6, §7 on page 189, first two paragraphs; D14, page 280, "Uses of Colors in Tablet Dosage Forms"; D15, middle column, "Colorants include ferric oxide" in the context of aripiprazole tablets). This purpose was also mentioned in the patent (see paragraph [0041]). The introduction of iron oxide into the coating of the tablet would thus be obvious.

In the Board's view, the skilled person could indeed introduce iron oxide in the tablet as a colorant. The presence of a colorant in the tablet is however not mandatory, and the appellant does not explain why the skilled person would choose iron oxide specifically among the various possible pigments. But above all, the appellant's argument based on the coloring properties of iron oxide does no justify that the skilled person would introduce iron oxide in the tablet in the expectation of solving the technical problem of improving photostability.

2.6.2 It is generally known that the use of pigments, such as iron oxides, titanium dioxide or aluminium lakes, in tablet coating can also protect and contribute to the stability of light-sensitive active materials in the tablet formulations (see D6, page 189, §7, 5th paragraph; D14, page 269, 1st paragraph, and page 280, 1st paragraph). However, neither D6 nor D14 lead to the particular choice of iron oxide or allow the skilled person to anticipate the particular technical effect obtained with this specific pigment, which is shown to be superior to titanium dioxide alone or in combination with aluminium lakes (see 2.4 above).

An inventive step may be acknowledged when a selection is connected to a particular technical effect, and no hint in the prior art leads the skilled person to this selection. Here, the selection of iron oxide is associated with a higher photoprotection of brexpiprazole compared with other common known alternatives. The prior art does not hint at the superior properties of iron oxide over other pigments. Contrary to the appellant's view, the selection involved is not out of two alternatives only, but out of a larger group of pigments with known

photoprotective properties (see the above cited passages of D6: "Pigments *such as* the iron oxides, titanium dioxide, and some of the aluminum lakes are especially useful for this purpose"; and of D14: "opaque color coats containing certain insoluble colors, *such as* titanium dioxide and iron oxides", emphasis added by the Board).

The appellant argued that any photoprotective pigment, including iron oxide, is a solution to the above technical problem, which is to improve photostability compared with the brexpiprazole tablet of D1 containing no pigment at all in the coating. According to the appellant, considering the generality of D1, the skilled person is free to use any pigment. The Board does not share this position. The choice made in claim 1 of the main request is not among equally suitable alternatives, but is a purposeful one. This choice leads to a technical effect even in comparison with embodiments which are not part of the prior art, but come closer to the claimed invention, such as the white, titanium dioxide-containing RXULTI tablets. Dismissing the effect of such a selection based on the generality of the closest prior art D1, as suggested by the appellant, would lead to the contradictory situation whereby an inventive step is denied because the prior art is not close enough.

Accordingly, the main request meets the requirements of inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Sánchez Chiquero A. Usuelli

Decision electronically authenticated