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Datasheet for the decision of 11 August 2020

Case Number: T 2582/17 - 3.3.01

Application Number: 13169077.8

Publication Number: 2656844

IPC: A61K31/436, A61K31/4745, A61P35/00

Language of the proceedings: EN

Title of invention:
Antineoplastic combinations containing HKI-272 and vinorelbine

Patent Proprietor:
Wyeth LLC

Opponent:
Generics [U.K.] Limited

Headword:
Combinations of HKI-272 and vinorelbine / WYETH

Relevant legal provisions:
EPC Art. 100(b), 100(a), 56
RPBA Art. 12(4)

Keyword:

Main request - sufficiency of disclosure over entire scope of the claim (yes)

Main request - inventive step - non-obvious alternative (yes)

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Beschwerdekammern

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Case Number: T 2582/17 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 August 2020

Appellant: (Opponent)	Generics [U.K.] Limited Station Close Potters Bar Herfordshire EN6 1TL (GB)
Representative:	FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Respondent: (Patent Proprietor)	Wyeth LLC 235 East 42nd Street New York, NY 10017 (US)
Representative:	Jones Day Rechtsanwälte, Attorneys-at-Law, Patentanwälte Prinzregentenstrasse 11 80538 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 25 September 2017 rejecting the opposition filed against European patent No. 2656844 pursuant to Article 101(2) EPC**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	S. Albrecht
	M. Blasi

Summary of Facts and Submissions

I. European patent No. 2 656 844 ("the patent") is based on European patent application No. 13 169 077.8 ("application as filed"). The patent was granted on the basis of a set of fifteen claims.

Claim 1 as granted is the sole independent claim and reads as follows:

"1. A pharmaceutical pack for use in a method for treating a neoplasm in a subject, said pharmaceutical pack comprising a first compound selected from (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide, an ester, ether, carbamate or pharmaceutically acceptable salt thereof and a second compound selected from vinorelbine or a pharmaceutically acceptable salt thereof, wherein said first compound is in a unit dose and wherein the unit dose contains 50 to 300 mg of said first compound."

II. Opposition proceedings were based on the grounds for opposition under Article 100(a) EPC for exclusion from patentability under Article 53(c) EPC, lack of novelty and lack of inventive step, and under Article 100(b) and (c) EPC.

The documents filed during the opposition proceedings included:

D3: "Lapatinib and Vinorelbine in Treating Women With HER2-Overexpressing Locally Advanced or Metastatic Breast Cancer", ClinicalTrials.gov Identifier: NCT00513058 (2014), U.S. NIH, pages 1-4

D8: Yun et al., PNAS, vol. 105, no. 6, 12 February 2008, pages 2070-5

D9: Hegde et al., Mol. Cancer Ther. 2007, 6(5), May 2007, pages 1629-40

D10: McNeil C., Journal of the National Cancer Institute, vol. 98, no. 16, 16 August 2006, pages 1102-3

III. The opponent's ("appellant's") appeal lies against the opposition division's decision to reject the opposition.

In the appealed decision, the opposition division found, *inter alia,*

(a) that the claimed invention was sufficiently disclosed,

(b) that the claimed subject-matter involved an inventive step having regard to the disclosure of document D10 relating to lapatinib as the closest prior art.

IV. In its statement setting out the grounds of appeal, the appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. The appellant also submitted, *inter alia,* the following evidence:

F2: "View of NCT00513058 on 2007_08_07", ClinicalTrials.gov archive, 7 August 2007, U.S. NIH, pages 1-4

V. In its reply to the statement setting out the grounds of appeal, the patent proprietor ("respondent") requested that the appeal be dismissed, and hence that the patent be maintained as granted (main request). The respondent further requested that document F2 not be admitted into the proceedings.

VI. The board issued a summons to oral proceedings in accordance with corresponding requests of the parties. In a communication pursuant to Article 15(1) RPBA 2020 issued on 3 June 2020, the board drew the parties' attention to the points to be discussed during the oral proceedings and provided, *inter alia*, a preliminary opinion acknowledging sufficiency of disclosure.

VII. With a letter dated 3 June 2020, the respondent filed six sets of claims of auxiliary requests 1 to 6 and requested that the objections raised by the appellant in its statement setting out the grounds of appeal pursuant to Article 100(c) EPC and Article 100(b) EPC regarding the choice of a particular dosage regimen not be admitted into the appeal proceedings.

VIII. In a letter dated 30 July 2020, the appellant informed the board that it would not be attending the oral proceedings.

IX. On 11 August 2020, oral proceedings took place in the presence of the respondent; the board decided to admit document F2 into the proceedings. At the end of the oral proceedings, the chairwoman announced the board's decision.

X. The appellant's written submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Main request - Sufficiency of disclosure

The claimed invention lacked sufficiency of disclosure in that it could not be performed over the whole range claimed. The suitability of the claimed combination of HKI-272 and vinorelbine for the treatment of benign neoplasms and neoplasms other than those arising from lung cell lines was neither taught in the application as filed nor derivable from the prior art.

Main request - Inventive step

The claimed subject-matter was obvious based on documents D3 or F2 as the closest prior art. However, even if the disclosure of document D10 relating to lapatinib were to be taken as the closest prior art, the claimed subject-matter would nonetheless have been obvious to the person skilled in the art having regard to this prior art in combination with the teaching of document F2. In particular, document D10 disclosed that HKI-272 (i.e. the first compound recited in claim 1) was more effective than lapatinib because of its irreversible mode of action on the HER2 receptor. Furthermore, the skilled person would have learned from document F2 that anti-HER2 agents such as lapatinib could be combined with vinorelbine to treat neoplasms, and that this combination treatment might kill more tumour cells. Consequently, the skilled person would have followed the teachings of documents D10 and F2 with a reasonable expectation of solving the problem posed, and would thereby have arrived at the claimed subject-matter in an obvious manner.

XI. The respondent's written and oral submissions, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of appellant's objections raised in its statement setting out the grounds of appeal pursuant to Article 100(c) EPC and Article 100(b) EPC (see point VII. above)

These objections had not been considered by the opposition division, and therefore constituted amendments within the meaning of Article 12(4) RPBA 2007. There were no apparent reasons - and the appellant had not named any - why these objections could not have been raised in the opposition proceedings. Accordingly, these amendments should not be admitted into the appeal proceedings.

Main request - Sufficiency of disclosure

The appellant did not present any arguments or evidence that would raise serious doubts about the suitability of the claimed combination for treating neoplasms. Therefore its objection should be rejected for this reason alone. The application as filed, on the other hand, provided *in vitro* and *ex vivo* data showing a therapeutic effect that was directly linked to the claimed use. In addition, the compounds of the claimed kit were known cancer therapeutics. Accordingly, it was *prima facie* credible that the claimed kit was suitable for treating any neoplasm.

Main request - Inventive step

The claimed subject-matter differed from the closest prior art - the disclosure of document D10 relating to lapatinib - in that a combination of HKI-272 and vinorelbine or a pharmaceutically acceptable salt thereof was used, the HKI-272 being in a unit dose containing 50 to 300 mg of this compound. The objective technical problem to be solved by the claimed invention was the provision of an alternative anticancer therapy. The proposed solution, i.e. the combination therapy in accordance with claim 1, was not rendered obvious by the cited prior art. The passage of document D10 referred to by the appellant in the context of obviousness was merely speculative and not generally applicable to all types of neoplasm. In addition, the skilled person would have been aware of safety concerns with irreversible tyrosine kinase inhibitors, as evidenced by document D8. Accordingly, the skilled person would not have considered irreversible tyrosine kinase inhibitors, including HKI-272, as an appropriate alternative to lapatinib for the treatment of neoplasms.

XII. The parties' final requests, in so far as they are relevant to the present decision, were as follows:

(a) The appellant requested in writing that the decision under appeal be set aside and the patent be revoked in its entirety, and that document F2 be admitted into the proceedings.

(b) The respondent requested that the appeal be dismissed, or alternatively that the patent be maintained in amended form on the basis of one of the sets of claims of auxiliary requests 1 to 6

filed with its letter dated 3 June 2020. The respondent also requested *inter alia* that document F2, and also the following objections raised by the appellant in its statement setting out the grounds of appeal, not be admitted into the proceedings:

(i) the objection against claim 1 as granted under Article 100(c) EPC,

(ii) the objection under Article 100(b) EPC regarding the choice of a particular dosage regimen.

Reasons for the Decision

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

2. Absence of the appellant from the oral proceedings

2.1 The appellant had been duly summoned but had chosen not to attend the oral proceedings, as announced in its letter of 30 July 2020.

2.2 In accordance with Rule 115(2) EPC and Article 15(3) RPBA 2020, the board decided to continue the proceedings in the appellant's absence and to treat the appellant as relying on its written case. By absenting itself from the oral proceedings the appellant has given up the opportunity to make any further submissions on the relevant issues of the case. Hence the board was in a position to announce a decision at the conclusion of the oral proceedings, as provided for in Article 15(6) RPBA 2020.

3. Admission of the appellant's objection pursuant to Article 100(c) EPC and the objection under Article 100(b) EPC concerning the choice of a particular dosage regimen (Article 12(4) RPBA 2007)

3.1 In its statement setting out the grounds of appeal, the appellant raised an objection of added subject-matter against claim 1 of the main request. In its view, the present application as filed disclosed solely pharmaceutical packs comprising vinorelbine in the form of "at least one unit dose". By contrast, the pharmaceutical pack of claim 1 included vinorelbine or a pharmaceutically acceptable salt thereof in any form. As a result thereof, this claim constituted an impermissible intermediate generalisation.

Moreover, the appellant argued in its statement setting out the grounds of appeal *inter alia* that the application as filed did not provide any instruction or teaching regarding the choice of a particular dosage regimen, thereby placing an undue burden on the skilled person to try to put the claimed invention into practice.

3.2 With its letter dated 3 June 2020, the respondent requested that the board decide, exercising its discretion pursuant to Article 12(4) RPBA 2007, not to admit these objections into the appeal proceedings.

3.3 Article 12(4) RPBA 2007, second half-sentence, requires the board to take into account everything presented by the parties under Article 12(1) RPBA 2007 if and to the extent it relates to the case under appeal and meets the requirements in Article 12(2) RPBA 2007. However, according to Article 12(4) RPBA 2007, first half-sentence, the board has the discretionary power to

hold inadmissible facts, evidence and requests which could have been presented or were not admitted in the proceedings before the opposition division.

3.4 In the case at hand, the board agrees with the respondent that the alleged insufficiency of disclosure regarding the choice of a particular dosage regimen had never been brought up in the proceedings before the opposition division. The same holds true for the appellant's objection of added subject-matter raised in its statement setting out the grounds of appeal, since the previously-presented objection concerning added subject-matter had been based on a different line of argument.

3.5 The board further notes that these objections are directed against claim 1 as granted, and thus could have been presented at an earlier stage. In addition, the appellant did not submit any reasons why these objections were not or could not have been filed during the opposition proceedings. It neither replied to the respondent's letter dated 3 June 2020 nor attended the oral proceedings.

3.6 Under such circumstances, the board decided, exercising its discretion pursuant to Article 12(4) RPBA 2007, to hold the aforementioned objections of the appellant relating to the grounds for opposition pursuant to Article 100(c) EPC and Article 100(b) EPC, put forward in the statement of grounds of appeal, inadmissible.

Main request

4. Article 100(b) EPC - Sufficiency of disclosure

4.1 Claim 1 of the main request is a purpose-limited product claim drawn up in accordance with Article 54(5) EPC. It is directed to a pharmaceutical pack for use in a method for treating a neoplasm in a subject, said pharmaceutical pack comprising

(a) a first compound selected from (E)-N-{4-[3-chloro-4-(2-pyridinylmethoxy)anilino]-3-cyano-7-ethoxy-6-quinolinyl}-4-(dimethylamino)-2-butenamide (HKI-272), an ester, ether, carbamate or pharmaceutically acceptable salt thereof, wherein said first compound is in a unit dose and wherein the unit dose contains 50 to 300 mg of said first compound,

and

(b) a second compound selected from vinorelbine or a pharmaceutically acceptable salt thereof.

4.2 According to the case law of the boards of appeal, attaining the claimed therapeutic effect is regarded as a functional technical feature of such claims. Hence, in order to meet the requirement of sufficiency of disclosure, the therapeutic efficacy of the composition must be credible across the scope claimed. On the other hand, an objection based on insufficient disclosure presupposes that there are serious doubts, substantiated by verifiable facts.

4.3 In the impugned decision, the opposition division had acknowledged sufficiency of disclosure on the ground

that the application as filed clearly set out both the pharmaceutical pack and its intended medical use based on the information and directions given in the application as filed (see point 7 of this decision).

4.4 In its statement setting out the grounds of appeal, the appellant had challenged the opposition division's finding on this issue (see point X. above).

4.5 The appellant's objection was subsequently addressed in the board's communication dated 3 June 2020. In item 4.2 of this communication, the board expressed a preliminary opinion acknowledging sufficiency of disclosure, observing *inter alia* that

(a) HKI-272 and vinorelbine had proven *in vivo* antitumour activity.

(b) Example 1 of the patent in suit demonstrated that the claimed combination inhibited the proliferation of lung cancer cells *in vitro*.

(c) Examples 2 and 3 of the patent in suit disclosed specific dosage regimens of the claimed combination in patients diagnosed with non-metastatic and metastatic breast cancer respectively.

(d) The appellant's objection as to insufficiency of disclosure did not appear to be substantiated by verifiable facts.

4.6 The appellant did not submit any facts or substantive arguments in reaction to the board's communication, and limited itself to confirming its requests and announcing that it would not attend the oral proceedings (see point VIII. above). Given these

circumstances, the board sees no reason to change its preliminary opinion.

4.7 It follows that the appellant's objection of insufficiency of disclosure pursuant to Article 100(b) EPC does not prejudice maintenance of the patent as granted.

5. Article 100(a) EPC in conjunction with Article 56 EPC

5.1 Admission of document F2 - Article 12(4) RPBA 2007

5.1.1 The respondent requested that document F2 - filed by the appellant together with its statement setting out the grounds of appeal - not be admitted into the appeal proceedings.

5.1.2 In the oral proceedings, the board decided to admit document F2 into the proceedings pursuant to Article 12(4) RPBA 2007 as it did not consider the respondent's arguments concerning the exclusion of this document from the proceedings convincing.

Closest prior art

5.2 According to established case law of the boards of appeal, the closest prior art is normally a prior art document disclosing subject-matter conceived for the same purpose as the claimed invention and having the most relevant technical features in common.

5.3 The patent is concerned with therapeutic regimens against neoplasms, more particularly solid tumours and metastatic breast cancer (see paragraphs [0008] and [0009]).

5.4 In its decision, the opposition division identified the disclosure of document D10 relating to the use of the EGFR inhibitor lapatinib as an antitumour agent as the closest prior art.

5.5 At the oral proceedings, the respondent agreed with this choice (see point XI. above). The appellant, on the other hand, identified document F2 or alternatively document D3 as the closest prior art.

5.5.1 Document D10 is a news report on EGFR inhibitors. It starts by describing the successful use of the dual-target agent lapatinib in the treatment of trastuzumab-resistant metastatic breast cancer. D10 then discusses younger generations of multi-target drugs by focusing on several key questions (see page 1102, left-hand column, final paragraph). Of these drugs, HKI-272 is described on page 1103, right-hand column, first full paragraph as an agent with promising activity in the treatment of advanced breast cancer and advanced non-small-cell lung cancer. However, the final sentence of the following paragraph states that the question of whether this drug is similar to lapatinib, and if so, how much better, remains to be answered. In light of this, the board agrees with the respondent that this teaching is a less-promising starting point than D10's disclosure relating to lapatinib.

5.5.2 Concerning documents F2 and D3, it is observed as follows:

As set out in the board's communication dated 3 June 2020 (see item 5.1.5(b) thereof), document F2 describes the set-up of a phase I clinical study evaluating the combination of lapatinib and vinorelbine in patients with locally advanced or metastatic breast

cancer overexpressing HER2. However, document F2 does not report any results with regard to this combination regimen.

Document D3 corresponds to a later version of document F2. In its communication dated 3 June 2020, the board noted that document D3 appeared to have been made available to the public not earlier than 13 January 2014 (see point 5.1.5(b) of this communication). Following this communication, the appellant did not submit any evidence in this respect. As a consequence, the board sees no reason to change its preliminary opinion, and therefore concludes that document D3 does not represent state of the art pursuant to Article 54(2) EPC.

5.5.3 It follows from the above that document F2 and the disclosure of document D10 relating to lapatinib come closest to the claimed invention. However, document F2 fails to disclose any results with regard to the lapatinib/vinorelbine combination regimen described therein. D10, on the other hand, reports on the success of lapatinib in the treatment of metastatic breast cancer in humans (see point 5.5.1 above). Given this background, the board agrees with the respondent that the disclosure of document D10 relating to lapatinib is a more promising springboard for the assessment of inventive step than document F2.

5.6 The subject-matter of claim 1 differs from the closest prior art in that a combination of HKI-272 and vinorelbine or a pharmaceutically acceptable salt thereof is used, HKI-272 being in a unit dose containing 50 to 300 mg of this compound.

Objective technical problem and solution

5.7 The board agrees with the respondent's formulation of the objective technical problem as the provision of an alternative anticancer therapy. This definition is substantially the same as the one provided by the opposition division in the impugned decision (see page 10, sixth full paragraph of this decision).

5.8 As a solution to this problem, the claimed invention proposes the combination recited in claim 1 (see point 4.1 above).

Obviousness

5.9 As argued by the appellant and accepted by the board, the following facts relating to lapatinib and HKI-272 were well known at the priority date of the patent:

(a) they are both tyrosine kinase inhibitors with identical targets, that is EGFR and HER2 (see page 1103, middle column, third full paragraph of document D10)

(b) they are used to treat similar cancers (see page 1629, right-hand column, third full paragraph of document D9)

(c) lapatinib is a reversible inhibitor of EGFR and HER2 (i.e. ErbB2), whereas HKI-272 irreversibly blocks these two receptors (see page 1629, right-hand column, second full paragraph of document D9)

5.10 In its statement setting out the grounds of appeal, the appellant contended that the subject-matter of claim 1

was obvious in the light of a combination of documents D10 and F2 (see point X. above).

5.10.1 In this context, the appellant referred in particular to the following passage of document D10, disclosed on page 1103, right-hand column, fifth full paragraph:

"For example, one difference among tyrosine kinase inhibitors is that some, like lapatinib, are reversible, whereas others, like HKI-272 and BIBW-2992, are irreversible - once the receptor is blocked it remains that way. This fact could make a difference in the drug's effectiveness, and Cohen noted that in preclinical studies, 'irreversibility has improved efficacy in specific molecular subsets, such as the EGFR vIII mutation, which is prominent in certain epithelial cancers.'"

5.10.2 In the appellant's view, the skilled person would have inferred from this teaching that irreversible tyrosine kinase ("TK") inhibitors such as HKI-272 are more effective than reversible ones, and would therefore have been motivated to replace the reversible TK inhibitor lapatinib with HKI-272.

5.11 The respondent counter-argued at the oral proceedings that the skilled person would have been aware of safety concerns relating to irreversible TK inhibitors, as evidenced by document D8, page 2074, right-hand column, second full paragraph. Furthermore, the statement in document D10 concerning the effectiveness of irreversible TK inhibitors was merely speculative. Accordingly, the skilled person would not have considered irreversible inhibitors including HKI-272 as an appropriate alternative to lapatinib for the treatment of neoplasms.

5.12 In the board's judgement, the skilled person would not have been prompted by the teaching of document D10 relied upon by the appellant to replace lapatinib with HKI-272.

5.13 Concerning the disclosure of document D8 referred to by the respondent the board notes the following.

5.13.1 Document D8 is a scientific paper on mutations in the EGFR tyrosine kinase published on 12 February 2008. Its content thus forms part of the skilled person's knowledge of TK inhibitors at the priority date of the patent.

5.13.2 The passage invoked by the respondent, i.e. page 2074, right-hand column, second full paragraph, reads as follows:

"As a class, irreversible inhibitors can overcome T790M resistance through covalent binding; once covalently bound, they are no longer in a competitive, reversible equilibrium with ATP. A number of such compounds are currently in clinical trials in oncology, including HKI-272, but none have yet received approval. One concern with covalent inhibitors is the potential for toxicity caused by off-target effects. At least 10 kinases in addition to EGFR have a reactive cysteine residue in the position equivalent to Cys-797 in EGFR, so it will be important to understand the activity of available irreversible agents against these kinases in particular, which include Tec family kinases, JAK3, and other kinases important for hematopoietic development and immune function."

5.13.3 The board agrees with the respondent that the skilled person reading this passage would have considered the potential for toxicity of irreversible TK inhibitors as rather high in view of the fact that the off-target effects of these compounds may involve a multitude of tyrosine kinases in addition to EGFR. Accordingly, based on this teaching, the skilled person would have adopted a particularly cautious attitude towards the use of irreversible TK inhibitors in the treatment of patients afflicted with neoplasms.

5.14 This cautiousness is also not outbalanced by the teaching of document D10 relied on by the appellant (see point 5.10.1 above). As convincingly argued by the respondent, the skilled person would have understood the statement of this passage concerning the effectiveness of irreversible TK inhibitors as speculative. Furthermore, the board is unable to find any other indication in this passage which might cause the skilled person to adopt a less-cautious attitude towards the use of irreversible TK inhibitors in oncology.

5.15 In view of the foregoing, the appellant's submissions fail to convince the board that the subject-matter of claim 1 is obvious over the cited prior art.

5.16 It follows that the appellant's objection of lack of inventive step pursuant to Article 100(a) EPC in conjunction with Article 56 EPC does not prejudice maintenance of the patent as granted.

6. The appeal must therefore be dismissed.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated