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Datasheet for the decision of 15 November 2024

Case Number: T 1090/22 - 3.3.07

Application Number: 10730454.5

Publication Number: 2451445

IPC: A61K9/20, A61K9/28, A61K31/517, A61J3/10, A61K9/16

Language of the proceedings: EN

Title of invention:
PROCESS FOR DRYING OF BIBW2992, OF ITS SALTS AND OF SOLID PHARMACEUTICAL FORMULATIONS COMPRISING THIS ACTIVE INGREDIENT

Patent Proprietor:
Boehringer Ingelheim International GmbH

Opponents:
Teva Pharmaceutical Industries Ltd
LEK Pharmaceuticals d.d.
Generics [UK] Ltd

Headword:
Dry BIBW2992/BOEHRINGER INGELHEIM

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - obvious alternative

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Beschwerdekammern

Boards of Appeal

Chambres de recours

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Case Number: T 1090/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 November 2024

Appellant: (Opponent 1)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
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Appellant: (Opponent 2)	LEK Pharmaceuticals d.d. Verovskova 57 1526 Ljubljana (SI)
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Appellant: (Opponent 3)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
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Respondent: (Patent Proprietor)	Boehringer Ingelheim International GmbH Binger Strasse 173 55216 Ingelheim am Rhein (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 10 March 2022 rejecting the opposition filed against European patent No. 2451445 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman A. Usuelli
Members: M. Steendijk
A. Jimenez

Summary of Facts and Submissions

I. European patent 2 451 445 ("the patent") was granted on the basis of ten claims.

Independent claim 8 as granted defines:

"A tablet comprising 4-[(3-chloro-4-fluorophenyl)amino]-6-{[4-(N, N-dimethylamino)-1-oxo-2-buten-1-yl]amino}-7-((S)-tetrahydrofuran-3-yloxy)-quinazoline in the form of its dimaleate (MA_2) salt (BIBW 2992 MA_2) as the active ingredient and at least one further excipient, characterized by a water activity of not more than 0.17."

The compound "BIBW 2992" has become known under the name afatinib.

II. Three oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as originally filed.

During the proceedings before the opposition division the patent proprietor filed its auxiliary request 1. Claim 8 of this auxiliary request corresponds to claim 8 as granted except that the water activity is defined as not more than 0.15.

The opposition division decided to reject the oppositions. The opponents filed appeals against this decision.

The opposition division cited *inter alia* the following documents:

D2: WO 2008/034776 A1
D4: Pharmaceutics - The Science of Dosage Form Design, 2nd edition, 2002, pages 379-383 and 441-445
D9: Die Tablette, 2nd edition, 2002, Chapter 4.4.4, pages 284-288
D11: WO 02/50043 A1
D19: United States Pharmacopoeia Chapter <1112>, 2009
D21: Submission of 30 January 2017 filed during the prosecution of EP 2 451 445 B1, including the annex "Supporting Experimental Data"

The opposition division concluded *inter alia* that the tablets characterized by the low water activity as defined in claim 8 as granted involved an inventive step over the tablets described in document D2 in view of their improved stability indicated by the experimental results reported in document D21.

III. In its communication under Article 15(1) RPBA the Board observed that document D21 seemed to indicate that coated tablets containing BIBW 2992 MA_2 which are conventionally prepared and not subjected to subsequent drying will have a water activity of 0.24. The Board questioned whether document D21 demonstrated that the tablets with a water activity of not more than 0.17 as defined in claim 8 as granted have improved stability over tablets which are conventionally prepared according to document D2, because the results from the stability study in document D21 do not seem to show any difference in the stability of tablets with a water activity of 0.15 as compared to tablets with a water activity of 0.25. The Board expressed its preliminary

opinion that the tablets of claim 8 as granted seem starting from tablets as conventionally prepared according to document D2 obvious as solution to the problem of providing alternative tablets.

IV. Oral proceedings were held on 15 November 2024.

V. The arguments of the opponents relevant to the present decision are summarized as follows:

The subject-matter of claim 8 as granted lacked an inventive step in view of document D2 as the closest prior art. Document D2 disclosed a method for the preparation of coated tablets containing 75 mg of active substance and described BIBW 2992 MA_2 as a preferred active substance. The difference of the subject-matter of claim 8 as granted with this prior art only concerned the feature of a water activity of not more than 0.17. Document D21 indicated that conventionally prepared coated tablets comprising BIBW 2992 MA_2 have a water activity of 0.24. The experimental results in document D21 did not demonstrate superior stability for tablets with a water activity of not more that 0.17 as defined in granted claim 8 over the conventionally prepared tablets with a water activity of 0.24. The objective technical problem underlying the subject-matter of claim 8 could therefore only be seen in the preparation of an alternative tablet. The provision of a tablet with a water activity of not more than 0.17 represented an obvious solution to the skilled person, because it was common general knowledge that a residual absolute moisture level of 1-2% in granulates may provide optimal compacting properties and that practical values for the water activity of solid pharmaceutical compositions may typically range from 0.2 to 0.6. It

was evident from the examples in the patent as well as the results reported in document D21 that in tablets comprising BIBW 2992 or its dimaleate salt a water activity of less than 0.15 includes an absolute water content of 1-2%. The skilled person was on basis of the common general knowledge represented by documents D4 and D9 well able to achieve the low water activity as defined in claim 8 by applying commonly known drying procedures.

The limitation to tablets with a water activity of not more than 0.15 in claim 8 of auxiliary request 1 did not overcome the objection of lack of inventive step against claim 8 as granted. Document D21 did not demonstrate an improved stability for tablets with a water activity of not more than 0.15 over the conventionally prepared tablets with a water activity of 0.24. The tablets of claim 8 of auxiliary request 1 therefore lacked an inventive step for the same reason as the tablets of claim 8 as granted.

VI. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

Document D2 described the therapeutic utility of a first active agent selected from BIBW 2992 and salts thereof, preferably the dimaleate (MA_2) salt, which could be combined separately or together with a further chemotherapeutic agent in a wide variety of pharmaceutical compositions, including solutions or suspensions in an aqueous liquid. Document D2 further presented examples of methods for the preparation of tablets comprising an active substance without specifying BIBW 2992 MA_2 as the active substance and without requiring any particular limit to the water activity of the tablets. The example presented in

document D2 for the preparation of coated tablets failed to provide any instruction regarding the drying conditions. Moreover, as reported in document D21, the preparation of tablets using BIBW 2992 MA_2 as the active agent required further deviations from the actual instructions described in the examples of document D2. Document D19 indicated in this context that it was common knowledge that a representative value for the water activity value of compressed tablets was 0.36.

Starting from the selection of BIBW 2992 MA_2 as the active compound the difference between the teaching in document D2 and the subject-matter of claim 8 as granted therefore concerned the formulation of BIBW 2992 MA_2 in a tablet as well as the requirement of the tablet having a water activity of not more than 0.17.

Document D21 demonstrated the enhanced stability of tablets containing BIBW 2992 MA_2 having a water activity of not more than 0.17 with respect to tablets with a higher water activity. The objective technical problem starting from document D2 therefore involved the provision of a pharmaceutical composition comprising BIBW 2992 MA_2 with improved stability.

The subject-matter of claim 8 as granted was not obvious as solution, because BIBW 2992 MA_2 had been reported to be highly stable and no prior art suggested enhanced stability from the formulation of BIBW 2992 MA_2 in a tablet having a water activity of not more than 0.17. Moreover, the prior art did not suggest how to prepare tablets comprising BIBW 2992 MA_2 having a water activity of not more than 0.17.

Document D21 indicated in this context that a standard manufacturing process for preparing coated tablets containing BIBW 2992 MA_2 could only provide tablets with a water activity of 0.24. This standard manufacturing process mentioned in document D21 did not relate to any method of preparing coated tablets described in the prior art, but instead only concerned an internal standard as applied by the patent proprietor. Document D21 further indicated that drying tablets for 24.5 hours at 20% relative humidity did not reduce the water activity of the tablets below 0.24 and that only unconventionally harsh conditions allowed for an adequate reduction of the water activity.

Claim 8 of auxiliary request 1 further specified the water activity of the tablets as not more than 0.15. This auxiliary request restricted the claimed subject-matter to tablets for which the experimental results presented in document D21 demonstrated an unexpected, enhanced stability over tablets with a water activity of 0.24. The subject-matter of claim 8 as granted was not obvious as solution to the problem of providing a pharmaceutical composition comprising BIBW 2992 MA_2 with improved stability, because no prior art suggested the enhanced stability of a tablet having a water activity of not more than 0.15 and because the prior art did not indicate how such tablets could be prepared.

VII. The appellants-opponents requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

VIII. The respondent-patent proprietor requested that the appeals be dismissed.

As an auxiliary measure, the patent proprietor requested that the patent be maintained on the basis of auxiliary request 1 as filed on 13 December 2021.

Reasons for the Decision

Main request

1. Claim 8 - Inventive step

2. Starting point in the prior art

2.1 Document D2 describes a method of treating patients suffering from cancer and harbouring mutations of EGFR in the tumour involving the administration of BIBW 2992, optionally in combination with a further chemotherapeutic agent (see D2, page 1, lines 1-6 and claim 1). Document D2 explains that the method of treatment comprises the administration of a therapeutically effective amount of BIBW 2992 or a pharmaceutically acceptable salt thereof, preferably the dimaleate (MA_2) salt (see D2, page 25, lines 22-27, under the heading "Method of treatment"). Document D2 thereby unequivocally discloses the use of BIBW 2992 MA_2 as preferred active substance for use in the described method of treatment.

Under the heading "Example 1: Coated tablets containing 75 mg of active substance" document D2 presents specific instructions for the production of coated tablets containing 75 mg of an active substance involving the preparation of tablets cores from defined amounts of specific excipients followed by the coating of these tablet cores with a film consisting

essentially of hydroxypropylmethylcellulose (see D2, pages 34-35).

From the disclosure of BIBW 2992 MA_2 as a preferred active substance in document D2 the skilled person derives directly and unambiguously that the process for the preparation of coated tablets described in example 1 of document D2 is in particular intended to prepare coated tablets containing BIBW 2992 MA_2.

Accordingly the coated tablets containing BIBW 2992 MA_2 prepared in example 1 represent within the teaching of document D2 a suitable starting point for the assessment of inventive step of the tablets defined in claim 8 as granted.

2.2 The patent proprietor argued that coated tablets containing BIBW 2992 MA_2 do not represent a suitable starting point disclosed in document D2, because document D2 does not specify the drying conditions for the coated tablets in example 1.

It is common knowledge that a process for preparing tablets involving the film coating of tablet cores inevitably includes a drying step (see D4, page 442, right column). The Board considers that in the absence of specific instructions regarding the drying conditions in the coating process described in example 1 of document 2 the skilled person understands that conventional drying conditions are to be applied. The lack of specific instructions concerning the drying conditions in example 1 of document D2 does therefore not disqualify this embodiment as a suitable staring point in the prior art.

2.3 The patent proprietor further contested that coated tablets containing BIBW 2992 MA2 represented a suitable starting point in document D2 in view of the evidence from document D21 that further deviations from the instructions in the examples of document D2 are required for the preparation of tablets when BIBW 2992 MA2 is used as the active substance.

The Board observes that according to document D21 the instructions for preparing tablets in "example 3 of D1" are not adequate when BIBW 2992 MA_2 is used as the active substance due to the hygroscopic properties of this compound (see D21, page 5 and page 10). The reference in document D21 to "example 3 of D1" concerns example 3 of document D11 in the numbering of the documents adopted in the appeal proceedings. The instructions in example 3 of document D11 are identical to the instructions in example 2 of document D2 and relate to the preparation of uncoated tablets involving a wet granulation process. The preparation of coated tablets according to example 1 of document D2 does not involve a wet granulation process. Any inapplicability of the wet granulation method of example 2 of document D2 for the preparation of uncoated tablets comprising BIBW 2992 MA_2 does therefore not disqualify the coated tablets containing BIBW 2992 MA_2 prepared according to example 1 of document D2 as a suitable starting point in the prior art.

3. Objective technical problem

3.1 The subject-matter of claim 8 as granted differs from the coated tablets containing BIBW 2992 MA_2 prepared in accordance with process of example 1 of document D2 by the feature that the claimed tablets have a water activity of not more than 0.17.

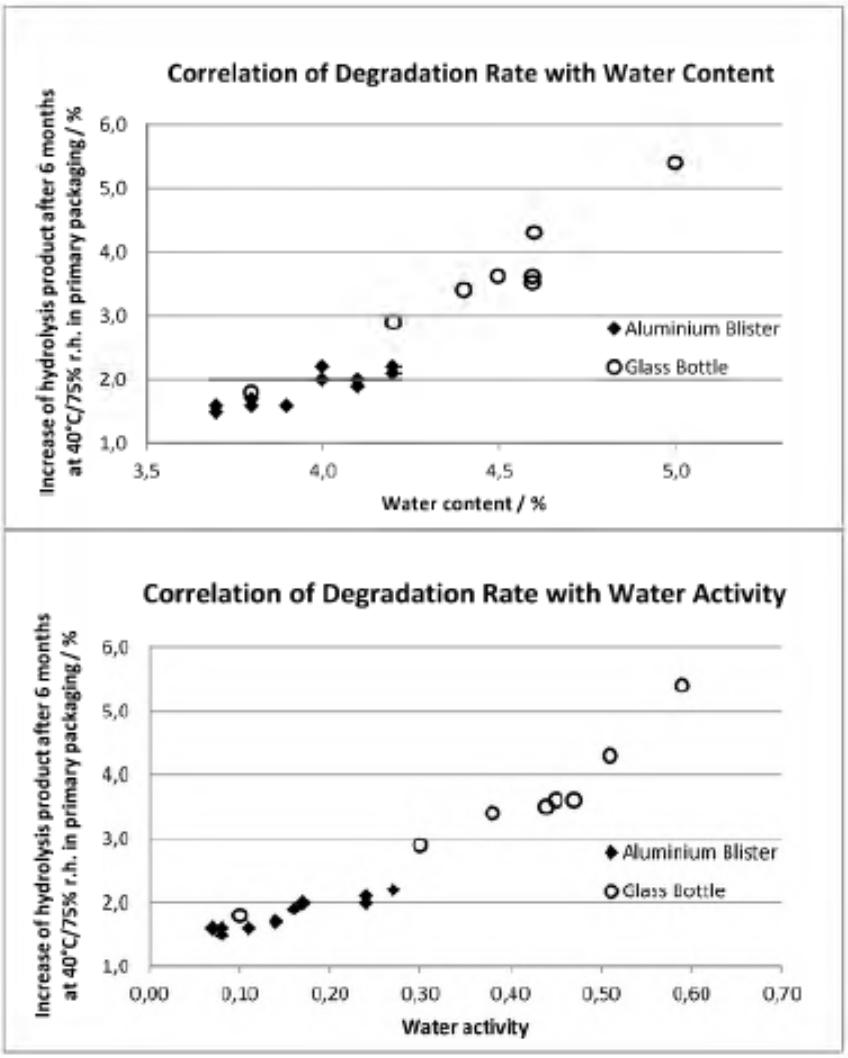
Example 1 of document D2 does not mention the water activity of the coated tablets resulting from the described preparation method and does not describe any particular drying conditions applied during the coating process of the tablet cores. However, as explained in section 2.2 above, the skilled person understands that in the absence of more specific instructions in example 1 of document D2 a standard manufacturing procedure involving conventional drying conditions is to be applied in the method of example 1 of document D2.

According to document D21 the standard manufacturing process for producing film-coated tablets containing BIBW 2992 MA_2 results in tablets having a water activity of 0.24 (see D21, page 6, lines 1-3 and page 11, Table under "Water Activity before Drying Step). The Board therefore concludes that the preparation of coated tablets containing BIBW 2992 MA_2 as the active substance in accordance with example 1 of document D2 and applying conventional drying conditions during the coating process results in tablets with a water activity of 0.24.

The patent proprietor argued that the reference to "the standard manufacturing process" in document D21 only concerned an internal standard as applied by the patent proprietor and that the water activity of 0.24 resulting from such process could therefore not be attributed to tablets prepared according to document D2. The Board observes, however, that document D21 describes in the identified passages film-coated tablets prepared by "the standard manufacturing process" as opposed to the tablets of the claimed invention having a reduced water activity due to

special drying (see page 6 and 11). Document D21 thereby clearly refers to a conventional process involving standard drying conditions during coating and not to a special process according to some internal standard. The patent proprietor's argument is therefore not considered convincing.

3.2 Document D21 further describes a stability study performed on film-coated tablets comprising BIBW 2992 MA2 within a wide range of values for the absolute water content as well as the water activity involving their storage in tight packaging materials (aluminium blister packings or glass bottles) over 6 months at 40°C/75% relative humidity (see D21, pages 7-9 and 12). The results of this study are presented in diagrams under the Headings "Correlation of Degradation Rate with Water Content" and "Correlation of Degradation Rate with Water Activity" (see D21, page 13). The diagrams indicate individual values for the percentage-increase of hydrolysis product (Y-axis) depending on the absolute water content and water activity (X-axis) by the entry of squares (aluminium blister) and circles (glass bottle). The diagrams are reproduced as follows:



Document D21 does not provide any particular statistical analysis with respect to the presented results. However, the presence of two squares having different values on the Y-axis, i.e. corresponding to different amounts of hydrolysis product, for the same value of water activity (see the two squares at a water activity of about 0.08 and the two squares at a water activity of about 0.25) indicates that the measurement of the degradation at a given water activity is affected by variation. It is further observed that the determination of the precision of the reported results is limited by the size of the squares and circles

relative to the scale for the degradation and water activity in the diagram.

Taking account of the indicated variation and the limited precision of the presented results, the Board considers that the stability study reported in document D21 does not demonstrate any reduction in the level of degradation when the water activity in the tablets is lowered from about 0.25 to about 0.15. Accordingly, document D21 does not provide convincing evidence of an advantage of the tablets as defined in claim 8 as granted having a water activity of not more than 0.17 with respect to the conventionally prepared coated tablets for which document D21 reports a water activity of 0.24.

3.3 In the absence of evidence of any demonstrated advantage the Board formulates the objective technical problem underlying the subject-matter of claim 8 as granted as the provision of alternative tablets with respect to the coated tablets containing BIBW 2992 MA_2 conventionally prepared in accordance with example 1 of document D2.

4. Assessment of the solution

4.1 It is not in dispute that documents D4 and D9 represent common general knowledge in the relevant field of technology. Document D19 is an excerpt from the US Pharmacopoeia from 2009 and is therefore also considered to represent common general knowledge in the relevant field of technology.

Document D4 points out that drying is an important operation in pharmaceutical manufacture, because it is usually the last stage of manufacturing before

packaging where it is important to prevent product deterioration and to ensure free-flowing properties during use (see document D4, page 380, under "Introduction"). Document D4 explains that once the solid to be dried reaches its equilibrium moisture content with the ambient air the prolongation of the drying time will not further reduce its moisture content and that the only way to further reduce the moisture content is by reducing the relative humidity of the ambient air. According to document D4 this can on a large scale be achieved with an air-conditioning system and on a small scale with a desiccator, for instance using silica gel, which reduces the relative humidity to around 5-10%. Document D4 emphasizes that moisture may be quickly regained from the atmosphere after drying and that sealing is necessary if the aim is for a low residual moisture content in view of hydrolytic instability in the material. Document D4 further notes that tablet granules have superior compacting properties with a small amount (1-2%) of residual moisture (see D4, page 382, under "Loss of water from wet solids" and Figure 26.3).

Document D9 describes the water activity of a pharmaceutical solid, which is defined by the relative equilibrium humidity that arises from it, as a relevant alternative parameter in addition to the absolute moisture content (see D9, page 286, left column). Document D9 explains that the water activity influences the processing properties of granulates as well as the qualities of the tablets prepared therefrom and indicates in this context a practical window for the water activity of 0.2 to 0.6 (see D9, page 286, right column). Document D9 further points out that the temperature and relative humidity are important factors in the process for granulates. In this context document

D9 indicates that the drying is best carried out at temperatures between 35°C and 40°C (see page 284, right column) and that depending on the relative humidity of the ambient air the granulate will absorb or loss moisture until an equilibrium is reached (see page 284, right column and page 285, left column).

Document D19 reports for the water activity of compressed tablets a representative value of 0.36 (see D19, page 608, Table 2).

4.2 Faced with the objective technical problem of providing alternative tablets with respect to the coated tablets containing BIBW 2992 MA_2 as conventionally prepared in accordance with example 1 of document D2 the skilled person may rely on the common general knowledge as represented in documents D4, D9 and D19.

On the basis of this common general knowledge the skilled person would be aware that that practical values for the water activity of solid pharmaceutical compositions may typically range from 0.2 to 0.6. (see D9, page 286, right column and D19, page 608, Table 2) and that granulates with a residual moisture of 1-2% may provide superior compacting properties (see D4, page 382, right column). In view of the mentioned lower value of 0.2 for typical values of the water activity the skilled person would consider a water activity of 0.17 still within the range of typically suitable values. Moreover, the results of the stability studies in document D21, in which the correlation of the degradation with the water activity as well as the water content are presented (see section 3.2 above) indicate that as a matter of fact a water activity of less than 0.15 in tablets comprising BIBW 2992 MA_2 may still include a water content of 1-2%. In view of the

common general knowledge the skilled person would therefore expect tablets containing BIBW 2992 MA_2 with a water activity of not more than 0.17 to represent suitable alternatives to the coated tablets containing BIBW 2992 MA_2 as conventionally prepared in accordance with example 1 of document D2.

Moreover, having regard to the common knowledge that the loss of moisture from a pharmaceutical composition will continue during drying until the equilibrium moisture content with the ambient air is reached the skilled person would be aware that in order to achieve a water activity of not more than 0.17 the relative humidity of the drying air must be sufficiently reduced. The skilled person was therefore well able to determine suitable drying conditions for coated tablets containing BIBW 2992 MA_2 in order to reduce the water activity in the final tablets to not more than 0.17.

4.3 The patent proprietor argued that document D21 demonstrated that only unconventionally harsh conditions allowed for an adequate reduction of the water activity in tablets containing BIBW 2992 MA_2. Document D21 presents in this context the following results regarding the water activity of tablets following drying with air of 25°C at different levels of relative humidity (see D21, page 12):

Tablet Strength	Water activity after drying with air of 25°C and …		
	8% r.h. (8 hours)	15% r.h. (71.25 hours)	20% r.h. (24.5 hours)
20 mg	0.12	0.19	0.24
50 mg	0.12	0.20	0.24

The Board considers that the presented results are in line with the common general knowledge that during drying the loss of moisture may only continue until the equilibrium moisture content is reached. In this

context the Board further observes that drying conditions involving a relative humidity below 15% are by no means unconventional. To the contrary, such conditions correspond to the conditions during drying in a desiccator using the common laboratory desiccant silica gel, which reduces the relative humidity to around 5-10% (see D4, page 382, right column). The patent proprietor's argument is therefore not considered persuasive.

4.4 Accordingly, the Board concludes that the subject-matter of claim 8 as granted represents an obvious solution to the identified objective technical problem and does therefore not involve an inventive step.

Auxiliary request 1

5. Claim 8 - Inventive step

Claim 8 of auxiliary request 1 differs from claim 8 as granted in that the water activity is defined as not more than 0.15 instead of 0.17.

For the reasons presented in section 2.1 above, the coated tablets containing BIBW 2992 MA_2 as conventionally prepared according to example 1 of document D2 represent a suitable starting point in the prior art. As explained in section 3.1 above, the conventional preparation according to example 1 of document D2 is considered to result in tablets having a water activity of 0.24.

As pointed out in section 3.2 above, document D21 does not demonstrate any reduction in the level of degradation by lowering the water activity in the coated tablets from about 0.25 to about 0.15. Document

D21 does therefore not provide convincing evidence of an advantage of the tablets as defined in claim 8 of auxiliary request 1 having a water activity of not more than 0.15 with respect to the conventionally prepared coated tablets with a water activity of 0.24. In the absence of evidence of any demonstrated advantage of the subject-matter of claim 8 of auxiliary request 1 the objective technical problem is to be formulated as the provision of alternative tablets.

In line with the explanations in section 4.2 above, the skilled person would in view of the common knowledge (see D9, page 286, right column and D4, page 382, right column) consider a water activity of 0.15 still within the range of typically suitable values for solid pharmaceutical compositions. The skilled person would therefore on basis of the common general knowledge expect tablets with a water activity of not more than 0.15 to represent suitable alternatives with respect to the coated tablets containing BIBW 2992 MA_2 as conventionally prepared in accordance with example 1 of document D2.

In line with the explanations in section 4.2 above, the skilled person was well able to determine suitable drying conditions for coated tablets containing BIBW 2992 MA_2 in order to achieve a water activity in the final tablets to not more than 0.15 on the basis of the common general knowledge that the loss of moisture during drying continues until the equilibrium with the ambient air is reached.

Accordingly, the Board concludes that the subject-matter of claim 8 of auxiliary request 1 represents an obvious solution to the identified objective technical

problem and does therefore also not involve an inventive step.

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:

A. Vottner A. Usuelli

Decision electronically authenticated