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**Datasheet for the decision
of 7 November 2019**

Case Number: T 0918/16 - 3.3.01

Application Number: 03751344.7

Publication Number: 1561472

IPC: A61K45/06, A61K31/41, A61K31/13

Language of the proceedings: EN

Title of invention:
SOLID PREPARATION

Patent Proprietor:
Takeda Pharmaceutical Company Limited

Opponents:
Generics [UK] Limited
Dr Klusmann Peter

Headword:
Pioglitazone and metformin/TAKEDA

Relevant legal provisions:
EPC Art. 54, 56, 83, 123(2)

Keyword:

Novelty - main request (yes)

Inventive step - main request (yes)

Sufficiency of disclosure - main request (yes)

Amendments - added subject-matter (no)



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Case Number: T 0918/16 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 7 November 2019

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Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
29 February 2016 concerning maintenance of the
European Patent No. 1561472 in amended form.

Composition of the Board:

Chairman A. Lindner
Members: M. Pregetter
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 561 472 is based on European patent application No. 03751344.7, filed as an international application published as WO2004/030700.

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(1) "Basic Principles of Particle Size Analysis" by A. Rawle, Malvern Instruments Ltd., pages 1-8

(2) WO 98/57634

(3) WO 01/35941

(4) Ansel et al., "Pharmaceutical Dosage Forms and Drug Delivery Systems", 1999, page 66

(11) US 6,117,451

(14) Horiba Scientific, "A guidebook to particle size analysis", 2012, 32 pages

(15) Kitamori et al., J. Pharm. Pharmacol., 1979, 31, 501-504

(16) Lieberman, Lachman, Schwartz (eds.), "Pharmaceutical Dosage Forms: Tablets", vol. 1, 1989, pages 5 and 6

(17) Kelly et al., AAPS PharmSciTech, 2006, 7(2), Article 49, E1-E12

(18) COULTER®LS Series, retrieved from the Internet: <http://www.cyto.purdue.edu/cdroms/cyto2/6/coulter/>

ss000096.htm [retrieved on 17 June 2016], 4 pages

(19) Calculation, corresponding to Annex 2 of the minutes of oral proceedings before the opposition division, concerning "Insufficiency of claims", (re-)submitted with opponent 1's statement of grounds of appeal

(20) Johnson, Pharm. Acta Helv., 1975, 50(3), 60-63

(21) Olsson et al., Pharm. Res., 2001, 18(2), 203-210

(22) Sebhatu et al., Eur. J. Pharm. Sci., 1999, 8, 235-242

(23) Okor et al., Pharm. Pharmacol. Commun., 1998, 4, 511-513

(24) Particle size analysis - Laser diffraction methods, ISO standard 13320-1, 40 pages

III. European patent EP 1 561 472 was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step, was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and extended beyond the content of the application as filed.

The opposition division decided that auxiliary request 2, submitted by letter dated 10 November 2015, met the requirements of the EPC.

IV. Both opponents appealed against the opposition division's decision. With the statement setting out the grounds of appeal, appellant 1 (opponent 1) submitted

documents (17) to (23).

- V. With the reply to the statements setting out the grounds of appeal, the respondent (patent proprietor) indicated that its main request was auxiliary request 2, found to meet the requirements of the EPC by the opposition division, and submitted auxiliary requests 1 and 2.

Claim 1 of the main request reads as follows:

"1. A solid preparation having a phase wherein pioglitazone or a salt thereof and a biguanide are uniformly dispersed, the ratio of median size of said biguanide to the median size of said pioglitazone or a salt thereof being 0.5 to 15, the median size of the biguanide is 10 to 100 μm , the measurement of the median size being made with a laser diffraction particle distribution apparatus."

- VI. Oral proceedings before the board took place on 7 November 2019 in the absence of appellant 2 (opponent 2) as announced by letter of 14 June 2019.
- VII. The appellants' arguments, insofar as they are relevant to the present decision, may be summarised as follows. Appellant 2's arguments are summarised as presented in writing.

Admission of documents

Documents (17) to (19) were filed with the statement of grounds of appeal as a reaction to the finding of the opposition division that particle size determination by laser diffraction led to a particle size by volume and not by number. These documents were prima facie

relevant in that they showed that laser diffraction methods could be used to measure particle sizes by number.

Documents (20) to (23) were filed with the statement of grounds of appeal as a reaction to the acknowledgement of the presence of an inventive step by the opposition division. These documents were prima facie relevant in view of effects related to hardness or content uniformity of solid preparations. They were thus crucial for the outcome of the decision.

Amendments

The "gold standard" had to be applied for the assessment of the allowability of the amendments. In the present case, there was no individualised disclosure of the combination of all the technical features of claim 1 of the main request in the application as filed. The features were merely disclosed separately in different lists, such as lists referring to insulin sensitisers or comprising alternatives for median size ranges. The introduction of the measurement method was a further selection. The disclosure of the application as filed was either generic or very specific. No pointers in the passages cited by the respondent and the opposition division allowed these passages to be combined with the further technical features of claim 1.

Furthermore, the application as filed did not mention that the median size of the actives was measured with a laser diffraction particle distribution apparatus when the actives were in a solid preparation and when the median size of the biguanide was 10 to 100 μm . In the examples and in the comparative example the median

sizes of the components were measured before the components were combined to form a solid preparation. However, claim 1 defined in a crystal clear manner that the particle size was that of the actives as present in the finished solid preparation. It was not necessary to consider whether claim 1 was worded as a product-by-process claim.

The subject-matter of claim 1 of the main request extended beyond the content of the application as filed.

Sufficiency of disclosure

Defining the particle size as the median particle size and indicating that it might be by weight or by number presented the skilled person with two different principles for determining the median size. Median sizes by weight differed fundamentally from median sizes by number; see e.g. document (14). By not defining which median size was to be taken, the patent in suit did not provide the skilled person with even one way to carry out the invention. The person skilled in the art could thus not solve the problem of the invention. The introduction of a measurement method using a laser diffraction particle distribution apparatus did not overcome the fundamental insufficiency of disclosure. Firstly, the patent in suit itself indicated that median size could be either derived from weight distributions or number distributions and that such median sizes could be measured using a laser diffraction particle distribution apparatus (paragraph [0018]). Secondly, documents (1) and (14), representing common general knowledge, disclosed that it was possible to convert the median size volume distributions measured with a laser diffraction apparatus into median size number

distributions. Such a conversion was a matter of routine; see documents (17) and (18).

Furthermore, the application as filed did not provide any information on how the median size should be measured using the laser diffraction particle distribution apparatus. There were several variables in the method that impacted upon the median particle distribution obtained, such as the relationship between the particle sizes and the wavelength of the laser used, the scattering efficiency of particles of different sizes and the degree to which the particles transmitted light (see document (1), pages 7 and 8). It was also not disclosed how to measure the particle sizes within the solid preparation, which was further complicated by the fact that the particles might change size upon compression. Additionally, median size was an inappropriate parameter since a certain median particle size could be achieved by particles with a wide range of different distributions. In view of the intended use of the solid preparations as pharmaceutical compositions such variations were unacceptable. Claim 6 of the main request defined an effect - a coefficient of variation of not more than 6% - which could not be achieved by certain particle size distributions (i.e. by distributions having a small number of very large particles together with a large number of very small particles). Moreover, the patent in suit failed to mention that the measurements of the particle sizes were reproduced. It was thus not clear whether the measurements underlying the original examples were reproducible and could teach the skilled person how to carry out the invention.

Novelty

As already established by the opposition division, documents (2) and (3) disclosed compositions comprising pioglitazone and a biguanide uniformly dispersed in a single phase (decision under appeal, points 1.2, 1.3 and 2.1). The patent in suit indicated that commercially available products having the desired median sizes could be used as the active agents (paragraphs [0018] and [0032]). It was thus clear from the patent in suit that these commercially available products actually had the required particle sizes. The method did not confer any technical feature on the solid preparation of claim 1 of the main request, which was consequently not novel.

Inventive Step

Documents (2) and (3) were equally suitable as the closest prior art. The differences between document (2) or (3) and the subject-matter of claim 1 of the main request were the median size of the biguanide, the ratio of median sizes of pioglitazone and biguanide, and the measurement method. These differences were, however, not linked to a technical effect, at least not over the whole scope of the claim. It was acknowledged in the patent in suit and by document (15) that the median size of the actives might change during compression. As a consequence of this change in particle size, median sizes of the starting materials could, in principle, not account for effects determined in the compressed tablets, as was done in the examples of the patent in suit. It was furthermore to be noted that example 1 had less content uniformity than examples 2, 3, 5 and 6 (see Table 1). The subject-matter of claim 1 of the main request was not limited

to tablets either. Therefore, effects related to the hardness of tablets were not relevant over the whole scope of the claim. There was no teaching in the patent that any effects were linked to the choice of pioglitazone and biguanide as active agents.

The technical problem had to be formulated as the provision of an alternative preparation or, in an alternative way, as the provision of solutions to various partial problems of solid preparations.

Common general knowledge, in the form of documents (4) and (16), taught the use of ingredients of similar particle sizes in solid preparations and identified a particle size within the range of 10 to 40 μm as "preferable" (see document (16), page 5, second full paragraph and paragraph bridging pages 5 and 6). When employing all ingredients at the same particle size of 10 to 40 μm , the skilled person would automatically make use of a biguanide having a size within the range of 10 to 100 μm and would concomitantly, using the further ingredients including the second active, pioglitazone, in the same particle size range, arrive at a ratio of 0.5 to 15 of median sizes of the two actives. Furthermore, document (11) explicitly emphasised that particle sizes are to be maintained "within a range that allows homogeneity of the powder mix" (paragraph bridging columns 7 and 8). The skilled person was thus directly led to the subject-matter of claim 1 of the main request, which, consequently, did not involve an inventive step.

VIII. The respondent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

Admission of documents

Documents (17) to (19) were not more relevant than the documents already on file. These documents could and should have been filed before the opposition division.

Documents (20) to (23) were late-filed and should not be admitted since the object of the inventive step discussion had not changed since the opposition phase. The decision of the opposition division did not add anything that had not been in the proceedings before.

Amendments

Claim 1 of the main request was a combination of claims 4 and 5 as filed with page 4, lines 9 to 26, the specific examples, page 11, first paragraph and page 6, paragraph 3, all passages referring to the description as filed. The technical features were disclosed in combination.

Sufficiency of disclosure

Claim 1 of the main request was a product claim. A person skilled in the art could manufacture the claimed solid preparations. The appellant's objections related essentially to the reproducibility of the determination of the median particle sizes. Paragraph [0018] of the patent in suit defined the term median size and disclosed a laser diffraction particle distribution apparatus for use in determining this median size. A commercial apparatus was even identified. It was common general knowledge that laser diffraction methods led to particle sizes by volume (or by weight); see document (1), page 7, middle column and page 8, middle column, bullet points 3 to 5. The same could be derived from

ISO standard 13320-1 (provided as document (24)). Moreover, document (14) confirmed that the primary result from laser distribution measurements was a volume-based distribution and the default D50 was the volume median particle size (pages 4 and 6). Thus, taking common general knowledge into account the person skilled in the art were enabled to reproduce the invention. The skilled person knew that the conversion of particle sizes obtained by a measurement method based on laser diffraction to median sizes by number entailed large errors. This could be seen from document (14), page 6, last paragraph. The description furthermore taught that the particle sizes were to be determined for the starting materials and not for the final formulation. A claim interpretation requiring particle size determination in the finished product would be illogical from a technical point of view. It was thus irrelevant whether claim 1 was read as a product-by-process claim. Arguments based on a lack of reproducibility of specific measurements were irrelevant. It was common general knowledge that the reproducibility of measurements was part of the considerations related to any procedure, as could be seen from the last paragraph on page 12 of document (14).

Novelty

Document (2) neither disclosed the specific combination of pioglitazone and biguanide nor a solid preparation containing these two actives in uniform dispersion. There was no indication of the particle size of the actives or of a ratio of their median sizes. Document (3), due to stability considerations, dispersed the thiazolidinedione compound and metformin within separate pharmaceutically acceptable carriers.

There were thus two phases in the composition, and consequently no phase in which pioglitazone and biguanide were uniformly dispersed together. Furthermore, there was no disclosure of particle sizes or ratios thereof.

Inventive step

When starting from either document (2) or (3) as the closest prior art, there were several differences. Apart from the fact that these documents did not disclose any particle sizes or ratios thereof, there was also no disclosure that the two actives were uniformly dispersed in one phase. The effects due to the differences were superior content uniformity and hardness of the solid preparation. These effects were shown in Tables 1 and 2 of the patent in suit. The technical problem could be seen as the provision of a solid preparation comprising pioglitazone and a biguanide that had higher dissolution properties, less variation in content and, when in tablet form, improved hardness. The solution as claimed in claim 1 of the main request was not obvious. Document (2) aimed at a totally different problem, i.e. the provision of an effective and safe treatment for diabetes mellitus. Document (3) focused on stability problems. The further documents invoked by the appellants, documents (4) and (16), were very general, did not concern pioglitazone and metformin (a compound having completely different dissolution properties from pioglitazone), and did not deal with combinations of actives. Document (11) even taught to use metformin with a particle size of 400-600 μm (column 8, lines 16 to 22). The respondents had made an *ex post facto* analysis. An inventive step was present.

IX. Appellant 1 (opponent 1) requested that the decision under appeal be set aside and that the European patent No. 1 561 472 be revoked.

Appellant 2 (opponent 2) had requested in writing that the decision under appeal be set aside and that the European patent No. 1 561 472 be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed (main request), or, alternatively, that the decision under appeal be set aside and the patent be maintained in accordance with the claims of auxiliary request 1 or 2 filed with the reply to the statement of grounds of appeal.

Reasons for the Decision

1. The appeals are admissible.
2. The oral proceedings before the board took place in the absence of appellant 2, who had been duly summoned but had chosen not to attend. According to Rule 115(2) EPC and Article 15(3) RPBA, the board was not obliged to delay any step in the proceedings, including its decision, by reason only of the absence at the oral proceedings of any party duly summoned who was treated as relying only on its written case. Hence, the board was in a position to announce a decision at the conclusion of the oral proceedings, as provided for by Article 15(6) RPBA.
3. *Admission of documents*
 - 3.1 *Documents (17) to (19)*

The board considers general theoretical considerations concerning mathematical, statistical and physical aspects of particle sizes and methods for measuring them to be within the common general knowledge.

Documents (17) to (19) confirm the information presented in the documents filed during the opposition proceedings. They were filed together with the statement of grounds of appeal (Article 12(2) RPBA). Consequently, the board has admitted these documents under Article 12(4) RPBA.

3.2 *Documents (20) to (23)*

Documents (20) to (23) relate to issues that have been invoked in the context of the discussion of inventive step, especially the relationship between particle sizes and hardness or content uniformity. Improvements of hardness and content uniformity were, however, the explicitly mentioned aim of the patent in suit (see paragraph [0006]). The filing of auxiliary requests during the opposition proceedings did not lead to any changes in this context.

Therefore, the opponents should and could have submitted these documents within the opposition period. Consequently, documents (20) to (23) have not been admitted (Article 12(4) RPBA).

4. *Claim 1 of the main request - interpretation*

Among the technical features of the main request, there are several which require interpretation.

4.1 *"having a phase wherein pioglitazone or a salt thereof and a biguanide are uniformly dispersed"*

A "phase" refers to a continuum in a certain physical state (in the present case solid) containing certain ingredients. A phase having two actives uniformly dispersed within it is thus to be interpreted as a continuum containing the two actives and possibly further ingredients. Dispersions of granules consisting of granules with different ingredients, i.e. one population of granules comprising pioglitazone (or salt thereof) and one population of granules comprising a biguanide, cannot be considered to represent a system having the two actives in the same phase.

4.2 *Point in time of determination of median particle size of ingredients*

Claim 1 of the main request defines a solid preparation having a phase in which the sizes of the two actives are ("being") in a certain ratio.

The passage using the term "being" in claim 1 starts off with the definition of a phase "wherein pioglitazone or a salt thereof and a biguanide are uniformly dispersed". The wording "are uniformly dispersed" renders it unclear whether the product claim contains a product-by-process feature or whether this term merely qualitatively describes the phase containing the active ingredients. Due to this lack of clarity it is necessary to consult the description of the patent in suit. It can be gained from the description of the patent in suit (with the same information being disclosed in the application as filed) that the particle sizes, and the ratio obtained from these, relate to the starting materials (see paragraphs [0017], [0032] and [0077]).

Consequently, the skilled person would understand that the median particle size of ingredients in claim 1 of the main request refers to the median size of the ingredients as such, i.e. before their introduction into the solid preparation.

4.3 *Median particle size when measured with a laser diffraction particle distribution apparatus*

In the context of the preparation of a pharmaceutical composition, the skilled person, i.e. in the present case a person experienced in preparing solid pharmaceutical compositions from starting materials which include particular substances, would know from common general knowledge that particle size measurements with a laser diffraction particle distribution apparatus provide as the direct result the median size by volume. Being aware that a conversion by calculation to a size by number may lead to large errors (see document (14), page 6, last paragraph), the skilled person would refrain from carrying out such a conversion unless explicitly directed to do so. The mere mentioning that particle size distribution may be a number distribution cannot be taken as an explicit prompt for such a conversion.

Consequently, the subject-matter of claim 1 is directed to median particle sizes based on a volume distribution (or a weight distribution).

5. *Amendments - Article 123 EPC*

5.1 Claim 1 of the main request has a basis in the following passages of the application as filed (references are to the A-publication):

Claim 5 of the application as filed, which defines the presence of a biguanide and refers directly to claim 4, can be combined with the median size of the biguanide as described in paragraph [0030]. The definition of the measurement method for the determination of the particle size is to be seen as a mere clarification (paragraph [0017]). The single selection necessary to arrive at the subject-matter of claim 1 of the main request is that of pioglitazone or a salt thereof from paragraph [0006].

The disclosure of the median size of biguanide in paragraph [0030] is made explicitly for the active ingredient biguanide. This particle size range is thus directly linked to the class of active ingredient defined in claim 5 of the application as filed. Thus, the introduction of the size range into claim 1 of the main request does not create a new combination of technical features.

The method of size measurement by a laser diffraction particle distribution apparatus is the only measurement method for particle sizes disclosed in the application as filed. The disclosure of paragraph [0017] is general disclosure and thus has to be understood as applying to all particle sizes described in the application as filed. The fact that this measurement method implies a certain type of particle size, i.e. median sizes by volume/weight, does not change the manner in which this method is disclosed. The introduction of a measurement method disclosed in such a general way into an independent claim does not lead to subject-matter extending beyond the content of the application as filed.

The introduction of pioglitazone or a salt thereof

stems from a single selection from the list of insulin sensitisers disclosed in paragraph [0006].

The subject-matter of claim 1 of the main request fulfils the requirements of Article 123(2) EPC.

- 5.2 The subject-matter of the dependent claims also has a basis in the application as filed. Metformin hydrochloride is the preferred biguanide and pioglitazone hydrochloride the preferred insulin sensitiser (see claim 6, paragraph [0013] and all the examples of the application as filed).

Dependent claims 6 and 7 define results to be achieved. While appellant 2 is correct in stating that these results are linked to the particle sizes, this link does not necessarily lead to a lack of support. The technical features of claims 6 and 7 are disclosed in a general way in paragraphs [0078] and [0080], respectively, of the application as filed. It is thus clearly derivable from the description as filed that all the solid compositions can be prepared in such a way as to arrive at the results defined in claims 6 and 7.

Appellant 2 has not provided any reasoned arguments why dependent claim 8, which has a basis in paragraph [0074] of the application as filed, contravenes the requirements of Article 123(2) EPC.

Consequently, the subject-matter of the dependent claims of the main request fulfils the requirements of Article 123(2) EPC.

5.3 The appellants made no objections under Article 123(3) EPC. The board has no objections either.

6. *Sufficiency of disclosure - Article 83 EPC*

Claim 1 of the main request defines a solid preparation. It is thus merely necessary to determine whether the patent in suit provides sufficient guidance for a skilled person to manufacture this solid preparation.

The appellants have focused their arguments on two main issues: the types of particle sizes and the change of particle sizes due to compression.

6.1 *Type of particle sizes*

The arguments provided by the appellants can be briefly summarised as follows. The choice of defining the particle size as the median size leads to huge variations, both due to the use of median sizes as such and due to the differences in actual values when comparing median size by number with median size by weight/volume. The skilled person are thus without any guidance as to which actual particles to use in order to prepare a composition suitable for use as a medicament.

The board points to the fact that claim 1 of the main request not only defines median sizes but also defines that said median sizes are to be measured with a laser diffraction particle distribution apparatus. As concluded under point 4.3 above, defining the measurement method using this type of apparatus implies the restriction to median sizes by volume (weight).

The skilled person were thus aware of which type of particle size to use.

It is a matter of fact that a median particle size does not provide any information concerning the particle size distribution. The appellants have, however, not contended that asymmetric particle size distributions play a role for the actives under consideration. It has not been argued that pioglitazone or a salt thereof and/or various biguanides, are prone to or do usually exhibit asymmetric particle size distributions, for example distributions that would provide few very large particles next to a large number of small particles. Furthermore, even if this theoretical possibility was actually present, the solid preparations as such could still be manufactured. In this context it is noted that there is no evidence on file that such a preparation would have a coefficient of variation above the upper limit defined in claim 6.

6.2 *Change of particle sizes due to compression*

Since the board has concluded that the particle sizes defined in claim 1 of the main request relate to the active ingredients as such, i.e. before their introduction into the solid preparation (see point 4.2 above), a potential change of particle size when manufacturing the claimed preparation cannot lead to a finding of lack of sufficiency of disclosure.

6.3 *Further arguments*

Appellant 2 further argued that no details of the laser diffraction method were disclosed. According to document (1), however, there were several important variables to be considered in laser diffraction

measurements. The board considers that a person skilled in the art would know how to select the appropriate parameters for carrying out measurements. Furthermore, the patent in suit explicitly mentions a certain apparatus (HELOS & RODOS; see paragraphs [0017] and [0099]). Variations in particle sizes due to different measurements methods or different measurement parameters are possible. Such variations fall within the ambit of clarity, which is not a ground for opposition.

Appellant 2 also mentioned the reproducibility of measurements. The board fails to understand how the failure of the patent in suit to "mention that the measurements of particle sizes were reproduced" (see statement of grounds of appeal, paragraph bridging pages 11 and 12) has an influence on sufficiency of disclosure.

6.4 In sum, defining particular active ingredients by a median particle size in the context of a product claim does not, in the present case, lead to a finding of insufficiency of disclosure.

7. *Novelty - Article 54 EPC*

Appellant 1 cited documents (2) and (3) as being novelty-destroying for the subject-matter of claim 1 of the main request.

7.1 Document (2) defines a composition comprising an insulin sensitiser, a biguanide antihyperglycaemic agent and a pharmaceutically acceptable carrier therefor (claim 14). From the list of insulin sensitisers in claim 22, pioglitazone can be selected. The combination of claims 14 and 22 fails to disclose a

particle size ratio, a particle size of the biguanide and the technical feature of the uniform dispersion of the two actives in one phase.

Concerning the particle sizes, appellant 1 argued that, according to the patent in suit (see paragraphs [0018] and [0032]), commercially available actives (here the pioglitazone and the biguanide) could be used and thus had to be understood as having the appropriate sizes. The board cannot agree with this argument. Both paragraphs cited by appellant 1 describe that the active agents can be pulverised. Consequently, not all commercially available active agents have the required particle sizes.

Furthermore, document (2) fails to disclose that pioglitazone (or its salt) and biguanide are uniformly dispersed in the same phase. Document (2) describes methods of either co-administration or sequential administration (page 2, lines 11 to 13). Co-administration includes administration of a formulation which includes both an insulin sensitiser and a biguanide or essentially simultaneous administration of separate formulations of each agent (page 2, lines 14 to 17). On page 5, lines 24 to 26, it is disclosed that compositions may be prepared by admixing an insulin sensitiser, the biguanide and a pharmaceutically acceptable carrier thereof. However no details are mentioned that would imply a uniform dispersion of the two actives in one phase, nor is the insulin sensitiser identified as pioglitazone (or a salt thereof). The opposition division cited three further passages - page 6, lines 27 to 32 and pages 10 and 11 - which allegedly showed that the two active compounds were uniformly dispersed. However, none of these passages explicitly discloses a uniform

dispersion of the two actives in the same phase. There is no implicit disclosure of such a dispersion either. The passage on page 6, lines 27 to 32, follows after two paragraphs dealing with dosage regimens. From both dosage regimens (see page 6, lines 19 to 22 and page 6, lines 23 to 26) it can be derived that the insulin sensitiser and the biguanide are in two distinct formulations, since the two actives are administered according to two different dosage regimens. These passages therefore concern co-administration. The passage cited by the opposition division immediately follows these disclosures of dosage regimens in the context of co-administration and specifies merely the distribution of "the active agent" (singular) in the solid oral composition. Pages 10 and 11 concern solid compositions comprising an insulin sensitiser in the form of rosiglitazone as the sole active, and do not concern compositions comprising both an insulin sensitiser and a biguanide. A uniform dispersion of both actives in the same phase thus cannot be derived directly, either explicitly or implicitly, from document (2).

- 7.2 Document (3) is aimed at the problem of providing compositions that inhibit or prevent instability due to the combination of active agents, especially rosiglitazone and metformin hydrochloride (page 1, lines 20 to 29).

Claim 1 of document (3) explicitly defines that the thiazolidinedione (which may be selected from a list to be pioglitazone) and the biguanide "are each dispersed within its own pharmaceutically acceptable carrier in the pharmaceutical composition".

Page 2, lines 19 to 21 describes that

thiazolidinedione/carrier mixtures are compacted with metformin hydrochloride/carrier mixtures to form a tablet. Here again, it is clearly stated that the thiazolidinedione has a separate carrier from the biguanide. When capsules are filled, thiazolidinedione and biguanide are separated in the same manner by providing two separate carriers for the two actives (page 2, lines 23 to 26). The mere fact that two granule populations are uniformly dispersed with each other does not mean that the two actives are present in the same phase. This can also be seen from all the examples of document (3). Furthermore, no particle sizes are disclosed in document (3).

- 7.3 Neither document (2) nor document (3) discloses all the technical features of claim 1 of the main request.

Claim 1 of the main request is novel (Article 54 EPC).

8. *Inventive step - Article 56 EPC*

- 8.1 The patent in suit relates to a solid preparation comprising an insulin sensitiser and a further active ingredient useful as a therapeutic drug for diabetes. Solid preparations superior in terms of the content uniformity of the insulin sensitiser and the preparation hardness can be obtained by uniformly dispersing both active components when producing a solid preparation (paragraphs [0001] and [0006]).

- 8.2 Documents (2) and (3) have been cited as the closest prior art. The disclosure of these documents has been discussed under points 7.1 and 7.2 above.

The subject-matter of claim 1 of the main request differs from the disclosure of these documents at least

in that pioglitazone or a salt thereof and a biguanide are uniformly dispersed in the same phase and on account of the ratio of median size of biguanide to pioglitazone or salt thereof and the particle size of the biguanide.

The respondent invoked effects concerning dissolution properties, hardness and content uniformity.

The impugned decision came to the conclusion that an effect based on dissolution properties could not be acknowledged since the patent in suit did not contain comparative data showing an improvement. No experimental evidence has been provided since. In the absence of data showing an effect concerning dissolution properties, such an effect cannot be acknowledged.

An effect based on hardness is shown in the patent in suit for tablets. The claims under consideration define solid preparations in general, i.e. including preparations in forms other than tablets, such as powders (possibly encapsulated) or granules (see paragraph [0042] of the patent in suit). An effect based on hardness has thus not been shown to be present over the whole scope of the claims under consideration.

An effect related to content uniformity is shown in Table 1 of the patent in suit. Several examples having two different ratios of median size of biguanide to pioglitazone or a salt thereof are compared with an example having a ratio outside the claimed range of ratios. It can be seen that the examples falling within the claimed subject-matter have a lower coefficient of variation of the two active agents. The size of the effect varies between different examples, but is in all

cases significantly different from the comparative example. An improvement of content uniformity is achieved.

- 8.3 The technical problem is thus the provision of a solid preparation comprising pioglitazone or a salt thereof and a biguanide having improved content uniformity.

The technical problem has been solved.

- 8.4 When starting from the closest prior art, the skilled person need to take two steps in order to arrive at the subject-matter of claim 1 of the main request. First, both actives have to be put in the same phase. Only once the decision to formulate both actives in the same phase has been taken does the question of the particle sizes of the two actives relative to each other gain any importance as a second step.

- 8.4.1 Document (2) aims at providing a combination of actives useful for the treatment of diabetes mellitus. It suggests using co-administration or sequential administration. There is, however, no concrete teaching concerning co-administration of the two actives by one solid preparation. The person skilled in the art, confronted with the problem of providing a composition having high content uniformity, is given no directions on how to formulate both actives in the same composition.

Formulating both actives in the same composition involves various considerations, including the interaction between actives and excipients, both from a chemical (e.g. stability considerations) and physical (e.g. dissolution properties) point of view.

Among these considerations is the selection of particle sizes. The board acknowledges that it can be seen from document (16) that there is a general recommendation, when formulating solid phases, to use an active and excipients having similar particle sizes. This recommendation is followed by the skilled person as can be seen from document (11) which discloses the same particle sizes for biguanide (metformin) and excipients (column 8, lines 2 to 6 and claim 1). Document (4) also stresses, in a more general way, the importance of particle sizes for solid preparations (page 66, left-hand column, third paragraph).

Apart from the considerations concerning particle sizes, however, further considerations are necessary. In the context of general stability considerations, excipients suitable for both actives have to be identified. Numerous further considerations have to be made. The appellants have submitted no documents that guide the skilled person towards formulating pioglitazone (or a salt thereof) and a biguanide in one solid preparation in which the two actives are in the same phase. On the contrary, document (3) clearly teaches away from formulating a thiazolidinedione-type drug, such as pioglitazone, in the same phase and with the same excipients as metformin, a commonly used biguanide (page 1, lines 20 to 29).

Consequently, the skilled person, starting from document (2) and faced with the technical problem defined in point 8.3 above, would not arrive at the claimed subject-matter.

- 8.4.2 Document (3) provides the clear guidance that, because of stability considerations, a thiazolidinedione, such as for example pioglitazone, and metformin

hydrochloride, a biguanide, are not to be formulated in the same phase. This guidance represents the core of the teaching of document (3) which thus teaches away from the subject-matter of claim 1 of the main request. A skilled person starting from document (3) would not arrive at the claimed subject-matter.

8.5 Thus, taking account of the arguments, facts and evidence put forward by the appellants, the subject-matter of the main request involves an inventive step.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated