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Datasheet for the decision of 2 June 2015

Case Number: T 0256/13 - 3.3.07

Application Number: 05795965.2

Publication Number: 1811957

IPC: A61K9/00, A61K9/20, A61K31/445, C07D211/32

Language of the proceedings: EN

Title of invention:

SOLID PHARMACEUTICAL COMPOSITION COMPRISING DONEPEZIL HYDROCHLORIDE

Patent Proprietor:

KRKA, tovarna zdravil, d.d., Novo mesto

Opponents:

Synthon B.V./Genthon B.V.
Forschner, Nina
Stada-Arzneimittel Aktiengesellschaft
Actavis Group PTC EHF
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DR REDDYS LABORATORIES (UK) LIMITED
Hexal AG
Teva Pharmaceutical Industries Ltd.
Appelt, Christian W.

Relevant legal provisions:

EPC Art. 56
EPC R. 99(1)(c)
RPBA Art. 12(4)

Keyword:
Admissibility of appeal - notice of appeal - request defining subject of appeal
Late-filed evidence
Inventive step - (no)

Decisions cited:
T 0358/08

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Case Number: T 0256/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 June 2015

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Party as of right: (Opponent 9)	Appelt, Christian W. Pettenkoferstrasse 20-22 80336 München (DE)
Representative:	Engelhard, Markus Boehmert & Boehmert Anwaltspartnerschaft mbB Patentanwälte Rechtsanwälte Pettenkoferstrasse 20-22 80336 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 21 December 2012 rejecting the opposition filed against European patent No. 1811957 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Semino
M.-B. Tardo-Dino

Summary of Facts and Submissions

I. European patent No. 1 811 957 was granted on the basis of 19 claims, independent claims 1 and 13 reading as follows:

"1. Solid pharmaceutical composition comprising donepezil hydrochloride in the form of a hydrate and excipients, and having a water content of 3 to 10 % by weight (determined by Karl Fischer)."

"13. Process for the preparation of the composition according to any one of claims 1 to 12 comprising mixing and processing donepezil hydrochloride and excipients to the desired composition."

II. Nine notices of opposition were filed in which revocation of the patent in its entirety was requested.

III. During opposition proceedings, the following documents *inter alia* were cited:

D2: EP-A-1 378 238
D6: WO-A-97/46527
D12: Brittain and Fiese, "Polymorphism in Pharmaceutical Solids", Chapter 8, pages 330-361
D17: WO-A-2008/012495
D18: Rowe et al., extracts from "Handbook of Pharmaceutical Excipients", 5th edition, 2005, pages 725-726, 389-394, 132-134, 336-337, 430-431
D19: Wade et al., extracts from "Handbook of Pharmaceutical Excipients", 2nd edition, 1994, pages 252-261, 84-87, 483-488, 223-228, 280-282
D21: Aricept® 10mg, patient information leaflet 2003
D22: Declaration of Maria Micallef dated 12 August 2009
D25: Declaration of Julie Burkitt dated 24 August 2009

D46: Certificate of analysis of Aricept® 5 mg tablets
D53: Extract from W. Ritschel et al., "Die Tablette", 2nd edition, pages 317, 318 and 297-299
D54: Extract from H. Liebermann et al., "Pharmaceutical Dosage Forms", 2nd edition, volume 1, 1989, pages 5-6

IV. The decision of the opposition division to reject the oppositions was announced at oral proceedings on 13 November 2012. As far as relevant to the present decision, that decision can be summarised as follows:

The solid pharmaceutical composition of claim 1 differed from the disclosure of D2, which was the closest prior art, in that donepezil hydrochloride was in the form of a hydrate (which was not the case for the amorphous form and the "crystalline form I" according to D2) and in that the water content was 3 to 10% by weight. The objective technical problem shown to be solved in the patent was the provision of a pharmaceutical composition of donepezil which is stable against polymorphic conversions and the solution provided by claim 1 was not obvious in view of the closest prior art in combination with D6 or any of the other evidence on file. The same conclusions applied to process claim 13.

V. Opponents 1, 3, 4, 5, 6, 7, and 8 (appellants) lodged an appeal against that decision. Opponents 2 and 9 are parties as of right.

With the statements setting out the grounds of appeal, the appellants submitted the following evidence:

appellant-opponent 1:
D56: H.G. Brittain, 1999, "Polymorphism in pharmaceutical solids", pages 1-10

D57: Jenkins et al., "Introduction to X-ray powder diffractometry", 1996, pages 23-26
D58: Declaration of Prof. Elias Vlieg dated 29 April 2013 and Annex 1 attached thereto

appellant-opponent 6:
D59: Tae-Joon Park et al., "Polymorphic Characterisation of Pharmaceutical Solids, Donepezil Hydrochloride by 13C CP/MAS Solid-State Nuclear Magnetic Resonance Spectroscopy", Bull. Korean Chem. Soc. 2009, volume 30(9), 2007, pages 2007-2010
D60: WO-A-2004/092137
D61: WO-A-2005/089511
D62: WO-A-2006/111983

appellant-opponent 4:
D63: decision T 1324/09
D64: decision T 0459/09

appellant-opponent 5:
D65: Test report: "Experimental Evidence of Instability"

appellant-opponent 8:
D66: Text of § 35 German Patent Act (PatG)
D67: Response of DPMA to file inspection request for priority
D68: Excerpt from "Lehrbuch der pharmazeutischen Technologie" (R. Voigt), 2nd Ed., 1975, pages 158-160
D69: Test report: stability of Aricept® and Yasnal® tablets under accelerated conditions
D70: Purchase receipt/packing slip for Aricept® tablets (Eisai/Pfizer)
D71: Purchase receipt/packing slip for Yasnal® tablets (Krka)

Additionally appellant-opponent 7 submitted with the letter of 18 December 2014 a further experimental report ("Stability of donepezil hydrochloride form I depending on conditions during granulation process", D73) and appellant-opponent 1 submitted with the letter of 27 May 2015 a second declaration by Professors Vlieg and De Gelder dated 27 May 2015 (D74) comprising 3 enclosed documents.

VI. In the reply to the statements setting out the grounds of appeal dated 20 November 2013 the patent proprietor (respondent) designated the claims as granted as the main request and filed first to tenth auxiliary requests, along with the following evidence:

D72: Letter from the Deutsches Patent- und Markenamt (DPMA) dated 5 October 2010.

Independent claim 1 of the first auxiliary request differed from that of the main request by the specification "wherein the donepezil hydrochloride is donepezil hydrochloride monohydrate and is of polymorphic form I".

Independent claim 1 of the second auxiliary request differed from that of the first auxiliary request by the limitation of the water content of the composition to "4 to 7 % by weight".

Independent claim 1 of the third auxiliary request differed from that of the second auxiliary request in that it is specified that the solid pharmaceutical composition "is in the form of a tablet".

Independent claim 1 of the fourth auxiliary request differed from that of the third auxiliary request in

that it is further specified that "the excipients include at least one diluent selected from microcrystalline cellulose and lactose monohydrate".

Independent claim 1 of the fifth auxiliary request differed from that of the third auxiliary request in that the following is further specified:
"wherein the water content of the donepezil hydrochloride hydrate and the various excipients used in the composition is adjusted in such a way that a migration of water from the excipients to the donepezil hydrochloride or vice versa is prevented, and wherein the composition comprises
(a) donepezil hydrochloride, and
(b) excipients, which are present in the composition in the amount of more than 11 % based on the total composition weight, and
(c) excipients, which are present in the composition in the amount of less than 11 % based on the total composition weight,
wherein the water content of excipients (b), in % by weight, minus the water content of active ingredient (a), in % by weight, is less than 4.0 % by weight (determined by Karl Fischer)."

Independent claim 1 of the sixth auxiliary request differed from that of the third auxiliary request in that the following is further specified:
"wherein the water content of the donepezil hydrochloride hydrate and the various excipients used in the composition is adjusted in such a way that a migration of water from the excipients to the donepezil hydrochloride or vice versa is prevented, and wherein the composition comprises
(a) donepezil hydrochloride, and

(b) excipients selected from lactose monohydrate, microcrystalline cellulose, powdered cellulose, dextrates (hydrated), lactitol (hydrated), siliconised microcrystalline cellulose, saccharose, calcium hydrogen phosphate, calcium carbonate, calcium lactate, or mixtures thereof, which are present in the composition in the amount of more than 20 % based on the total composition weight, and

(c) excipients selected from polyvinyl pyrrolidone, carboxymethylcellulose sodium, polacriclin potassium, starch, sodium starch glycolate, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose or other cellulose ethers, polymethacrylate, crospovidone, stearic acid, magnesium stearate, calcium stearate, sodium laurylsulphate, hydrogenated vegetable oil, hydrogenated castor oil, sodium stearyl fumarate, talc, macrogols, or mixtures thereof, which are present in the composition in the amount of less than 20 % based on the total composition weight,

wherein the water content of excipients (b), in % by weight, minus the water content of active ingredient (a), in % by weight, is less than 2.0 % by weight (determined by Karl Fischer)."

Independent claim 1 of the seventh auxiliary request differed from that of the third auxiliary request in that it is further specified that the donepezil hydrochloride monohydrate of polymorphic form I "has an average particle size of 5 to 300 µm" and the excipients "have a particle size of D90<500 µm".

Independent claim 1 of the eighth auxiliary request differed from that of the third auxiliary request by

the limitation of the water content of the composition to "5 to 6 % by weight".

Independent claim 1 of the ninth auxiliary request is directed to a process and reads as follows:

"1. Process for the preparation of a solid pharmaceutical composition, which is in the form of a tablet, comprising donepezil hydrochloride in the form of a hydrate and excipients, and having a water content of 3 to 10 % by weight (determined by Karl Fischer), wherein the donepezil hydrochloride is donepezil hydrochloride monohydrate and is of polymorphic form I, said process comprising mixing and processing donepezil hydrochloride and excipients by

(i) granulating a mixture of excipients using water as granulation liquid to give a granulate,

(ii) adding donepezil hydrochloride and excipients to the granulate to give a compression mixture,

(iii) compressing the compression mixture to the desired form, and

(iv) optionally applying a coating."

Independent claim 1 of the tenth auxiliary request differed from that of the ninth auxiliary request by the further specification "wherein the temperature of the mixture and of the granulate does not exceed 50°C during the granulating step and wherein the water content of the granulate is 0.5 to 2.5 % determined as loss on drying at 85°C, 20 minutes".

VII. In a communication sent in preparation of oral proceedings, the Board addressed *inter alia* the inventive step of the product claims of the main request. In particular, formulation of the objective technical problem in the light of the evidence on file

was discussed. Furthermore, it was noted that the water content cited in independent claim 1 of the main request appeared to be conventional in view of the evidence provided for the water content of the Aricept® tablets, which appeared to fall approximately in the middle of the claimed range, and the calculated water content values provided by numerous appellants in respect of examples 1 and 2 of D2.

VIII. Oral proceedings were held on 2 June 2015.

IX. The arguments of the appellants, insofar as relevant to the present decision, can be summarised as follows:

Admissibility of appeals

a) The notice of appeal of appellant-opponent 5, in contrast to the allegation of the respondent, contained a request defining the subject of the appeal, namely in the form of the statement "the opponent requests that the decision of the Opposition Division to maintain the patent as granted be set aside". Accordingly, the requirements of Rule 99(1)(c) EPC were fulfilled and the appeal was admissible.

Admittance of documents filed in appeal

b) Experimental report D65 should be admitted into the proceedings, as it had a probative value which was *prima facie* relevant to the validity of the patent.

The declaration D74 and the enclosures attached thereto were filed in reaction to the comments of the Board in the communication in preparation for

oral proceedings concerning the definition of the term "hydrate" and served to demonstrate the diverse use of the term in the art. They were therefore highly relevant to the issues at stake and should be admitted into the proceedings.

Inventive step - main request

c) D6 was one of a number of suitable closest prior art disclosures as it disclosed polymorphic forms of donepezil hydrochloride, including the polymorphic form I hydrate, as well as a general disclosure of pharmaceutical compositions comprising excipients in addition to the polymorphs, and was also concerned with the stability and hygroscopicity thereof. D6 differed from claim 1 of the main request in that it did not define the water content of said compositions, such that the distinguishing feature of claim 1 was the water content of from 3 to 10 wt%.

d) No evidence had been provided demonstrating that the defined water content led to improved stability, as alleged. According to example 4b in the patent, the absence of new peaks in the X-Ray Diffraction Pattern (XRDP) of the tablets which were subjected to stability testing was proof that there had been no polymorphic interconversion. However, the patent lacked comparative examples showing that the claimed compositions were more stable than corresponding compositions having a water content falling outside of the claimed range. Furthermore, none of the documents on file provided the required evidence, while D17, a post-published document which discussed the stability of compositions of polymorphic form I of donepezil

hydrochloride provided contrary evidence by concluding that the same compositions were stable even when the water content of the solid composition was less than 3 wt%. Despite the fact that the original challenge to the alleged evidence provided in the patent was already raised at the time of filing of the respective notices of opposition, no further proof of the alleged effect had since been provided. It followed that the inclusion of 3 to 10% by weight water in the solid composition of claim 1 was nothing more than an arbitrary step having no technical effect.

e) In view of the above, the objective technical problem was the provision of an alternative pharmaceutical composition comprising a hydrate of donepezil hydrochloride.

f) The solution provided by claim 1 was obvious in view of D6 in combination with the commercially available Aricept® tablets (manufactured both before and after the priority date of the patent) whose excipients were known from D21 and whose water content as determined by appellant-opponents 4 and 8 (D22, D25 and D46) fell in the range of 4.6 to 5.9 wt%. Alternatively the solution provided by claim 1 was obvious in view of D6 in combination with D2, which disclosed in example 1 a donepezil hydrochloride composition prepared by dry granulation comprising polymorphic form III of donepezil hydrochloride. It would be routine for the skilled person to use this example to prepare a composition comprising the form I hydrate, and the types and quantities of excipients in D2 would inevitably result in a composition having a water

content falling within the range recited in claim 1.

Inventive step - auxiliary requests

g) None of the auxiliary requests fulfilled the requirements of Article 56 EPC.

h) The arguments provided for the main request applied equally to the first to fourth auxiliary requests.

i) That the condition comprised within claim 1 of the fifth and sixth auxiliary requests, namely that the migration of water from the excipients to the donepezil hydrochloride or vice versa was prevented by limiting the difference in the water content of the donepezil hydrochloride hydrate and the various excipients to within a specific range, has actually been achieved, was not backed up by any evidence on file and consequently could not form the basis for acknowledging inventive step.

j) The specification of the particle size ranges of donepezil hydrochloride monohydrate and the excipients according to claim 1 of the seventh auxiliary request represented no more than a juxtaposition of conventional features which could not contribute to the acknowledgement of inventive step. The conventional nature of the chosen ranges was evident in view of the disclosures of D18 and D19 (for the excipients) and D54 (for the active substance).

k) The arguments in respect of claim 1 of the main request were equally valid for claim 1 of the eighth auxiliary request.

l) The processes of claim 1 of the ninth and tenth auxiliary requests comprised conventional process steps known from the prior art (see in particular D53, page 317, points 2 and 3). Furthermore, there was no indication that the specific process claimed led to any particular surprising effect. The temperature range added to claim 1 of the tenth auxiliary request was also conventional in view of the disclosure in D53 that granulation temperatures were normally in the range of 40 to 80°C. Furthermore, the water content of the granulate was conventional and arbitrary in view of D12, which disclosed that complete drying of the granulate might not be desirable, and in view of the requirement that, in any case, the final water content of the composition must fall within the claimed range.

X. The arguments of the respondent, insofar as relevant to the present decision, can be summarised as follows:

Admissibility of appeals

a) In contravention of the requirements of Rule 99(1)(c) EPC, the notice of appeal filed by appellant-opponents 5 and 6 did not contain a clear request defining the subject of the appeal. These appeals should consequently be deemed inadmissible.

Admittance of documents filed in appeal

b) The experimental reports D65 and D69 (filed by appellant-opponents 5 and 8 respectively with the statements setting out the grounds of appeal) should not be admitted into the proceedings as they were filed more than three years after expiry of the time limit for filing an opposition, and were thus late filed. Furthermore, said reports were not *prima facie* relevant.

The declaration D74 and the enclosures attached thereto should not be admitted into the proceedings as they were filed only a few days before oral proceedings. Said enclosures did not originate in the field of pharmaceuticals and were consequently irrelevant.

Inventive step - main request

c) Document D2, which was concerned with the problem of avoiding the polymorphic conversion of donepezil hydrochloride-containing pharmaceutical compositions, was the closest prior art. D2 described a solid pharmaceutical composition in which donepezil hydrochloride was in the amorphous state or in a crystalline form, the latter being retained during dry granulation. The composition differed from claim 1 of the main request in that the latter comprised donepezil hydrochloride in the form of a hydrate and had a water content of 3 to 10 wt%. The technical effect of avoiding the conversion of the polymorphic form during manufacture and storage was demonstrated by example 4 and figure 1 of the patent whereby the stability of tablets comprising donepezil

hydrochloride hydrate having a water content of 5.5 wt% was tested by determining the polymorphic form of donepezil hydrochloride by XRDP analysis. The objective technical problem was the provision of a solid pharmaceutical composition comprising donepezil hydrochloride which was stable against polymorphic conversion during manufacture and storage. It was not obvious in view of D2 alone or in combination with any other document to use donepezil hydrochloride in the form of a hydrate in combination with the specific water content of the composition as defined in claim 1 to solve the problem as posed.

d) Although D2 rather than D6 represented the closest prior art, should one consider that the skilled person would start from the latter document, the following would apply in respect of inventive step: the difference between claim 1 of the main request and the disclosure of D6 was that the latter did not teach or suggest a specific pharmaceutical composition comprising donepezil hydrochloride, nor such a composition having a water content of 3 to 10 wt%. The technical effect was demonstrated in example 4 of the patent, and the objective technical problem was consequently the provision of a solid pharmaceutical composition comprising donepezil hydrochloride which was stable against polymorphic conversion during manufacture and storage. The solution was not obvious in view of D6 alone or in combination with any of the other cited prior art documents, in particular D2 which taught the skilled person to either use an amorphous form of donepezil hydrochloride or "polymorphic form I" (which has been accepted by all parties as being identical to

polymorphic form III according to D6), which was anhydrous. Even in the event that the objective technical problem was considered as a mere alternative, which was denied, the combination of elements of claim 1 of the main request could not be derived from the prior art, as there was no implicit or explicit disclosure of a water content falling within the claimed range of 3 to 10 wt%, and thus the solution to the corresponding technical problem was equally not obvious.

Inventive step - auxiliary requests

e) Claim 1 of each of the first to fourth auxiliary requests was further distinguished from the subject-matter of the prior art D2 and D6 compared to claim 1 of the main request. The limitation in particular to a narrower water content range of from 4 to 7 wt% meant that the skilled person would be even less likely to inevitably obtain a water content falling within that range when preparing the compositions of the prior art.

f) Claim 1 of the fifth and sixth auxiliary requests, which comprised the condition that a migration of water from the excipients to the donepezil hydrochloride or vice versa was prevented by limiting the difference in the water content of the donepezil hydrochloride hydrate and the various excipients to a certain range, involved an inventive step since it was surprising that the specific polymorphic form I was stable as a result of said specific water content difference. The effect was demonstrated in example 4 of the patent, which fell under the scope of the claim. The further limitation in claim 1 of the sixth

auxiliary request to specific excipients chosen from lists in a specific amount further delimited the subject-matter of the claim from the prior art. Even if the objective technical problem were to be seen as the provision of an alternative process, the subject-matter of said claims was not derivable from the prior art.

g) Claim 1 of the seventh auxiliary request, which specified the donepezil hydrochloride monohydrate and excipient particle size range involved an inventive step since the specific combination of the water content and the specific particle size ranges was not derivable from the prior art.

h) Claim 1 of the eighth auxiliary request differed from claim 1 of the third auxiliary request in that the water content range was further limited to 5 to 6 % by weight, a very narrow range which would not be inevitably achieved on preparing the compositions of the prior art.

i) Claim 1 of the ninth and tenth auxiliary requests were directed to a process for the preparation of a solid pharmaceutical composition comprising donepezil hydrochloride monohydrate comprising specific process steps. The process steps in combination with the use of granulation techniques were not obvious starting from document D6, which did not disclose the preparation of a specific composition, because the process used was not conventional in the art. The technical effect thereof was that it led to a stable product as shown by example 4 of the patent. Claim 1 of the tenth auxiliary request, which in addition to the process steps of claim 1 of the ninth auxiliary

request comprised limitation to the temperature of the mixture and the granulate and the water content of the granulate was not derivable from a combination of documents D6 and D2.

XI. The appellants requested that the decision under appeal be set aside and the patent be revoked.

XII. The respondent requested that the appeals be dismissed, alternatively that the patent be maintained on the basis of one of the first to tenth auxiliary requests filed with the letter of 20 November 2013. The respondent further requested that the appeals of opponents 5 and 6 be rejected as inadmissible.

Reasons for the Decision

Admissibility of the appeal of opponents 5 and 6

1. The requirements of Rule 99(1)(c) EPC prescribe that the notice of appeal shall contain a request defining the subject of the appeal. According to the case law this is satisfied if the notice of appeal contains a request, which may be implicit, to set aside the decision in whole or, (where appropriate) only as to part; such a request has the effect of 'defining the subject of the appeal' within the meaning of Rule 99(1)(c) EPC (Case Law of the Boards of Appeal of the EPO, 7th edition 2013, IV.E.2.5.2 c), in particular decision T 358/08 of 9 July 2009).

1.1 In the present case the notice of appeal of opponent 5 states that "[t]he opponent requests that the decision of the Opposition Division to maintain the patent as granted be set aside". Similarly, the notice of appeal

of opponent 6 comprises the statement that the opponent "hereby appeals against the Decision dated 21 December 2012 by the Opposition Division to reject the opposition(s) against European patent EP1811957B. The Appeal is lodged against the Decision in its entirety".

1.2 In both cases the statement of the opponent can only be understood as a request to set aside in whole the decision of the opposition division to reject the oppositions and, as a necessary consequence, to revoke the patent. Accordingly, the requirements of Rule 99(1)(c) EPC are fulfilled. The Board has no doubt that all other formal requirements are met (which has not been contested by the respondent).

1.3 In view of that, the appeals of opponents 5 and 6 are admissible.

Admittance of the documents filed in appeal

2. Documents D65 and D69, whose admittance into the proceedings was contested by the respondent, were filed by appellant-opponents 5 and 8 with their statements setting out the grounds of appeal. These reports provided experimental tests in respect of the stability of solid pharmaceutical compositions of donepezil hydrochloride, a critical issue central to the decision of the opposition division in respect of inventive step, with reference in particular to the issue whether example 4 of the patent constituted evidence for the alleged technical effect. These documents were therefore timely filed by the appellants in appeal and can be seen as legitimate reactions to the decision, so that the Board sees no reason under Article 12(4) RPBA not to admit them. The same holds for documents D56-

D64, D66-D68 and D70-D72, which were filed with the statements of grounds or with the reply thereto and whose admittance was not contested by the opposing parties. On that basis documents D56 to D72 are admitted into the proceedings.

2.1 With regard to the the experimental report D73 and the declaration D74 (with 3 enclosed documents), which were filed after oral proceedings had been arranged, as they were not used in arguments relevant to the present decision, there is no need for the Board to decide on their admittance.

Main request - inventive step of claim 1

3. *Closest Prior art*

3.1 According to the decision under appeal and the respondent, D2 represents the closest prior art, while the appellants propose several suitable starting points for the skilled person, *inter alia* D2 and D6.

3.2 The decision under appeal does not explain why D2 should be seen as the closest prior art. The respondent on the other hand based his choice on the apparent observation that D2 and the contested patent both deal with the problem of avoiding polymorphic conversion of donepezil hydrochloride in pharmaceutical compositions.

3.3 However, polymorphic conversion is not mentioned at all in D2. D2 states that "The crystalline state of the active ingredient ... may play a significant role in the behaviour of the drug .. and may influence its therapeutical effect" (paragraph [0003]). Citing previous documents, it is stated that five different crystalline forms of donepezil hydrochloride are known,

and noted that it is important that the formulation contains the same crystalline form in order to ensure the same therapeutic activity (paragraph [0004]). Accordingly, it is said to be not easy to achieve this since, according to said cited documents, the procedures for producing the various forms are liable to result in a different form from that intended (paragraph [0005]).

3.4 Thus, according to D2, the difficulty with the known crystalline forms of donepezil hydrochloride was ensuring, during the preparation thereof, that the desired polymorphic form is indeed prepared. The conversion of one polymorphic form to another during or after said preparation is not addressed. On the other hand, D2 is concerned with the stability in terms of avoiding the development of impurities, and is based on the observation that in contrast to what is disclosed in previous documents, amorphous donepezil hydrochloride is stable to the production of such impurities over an extended period of time (paragraphs [0007] and [0008]).

3.5 D6 on the other hand discloses five polymorphic forms of donepezil hydrochloride (forms I to V) and processes for their production (starting on page 2 "Summary of the invention"). That polymorphic forms I and IV are hydrate forms has been acknowledged in the patent (paragraph [0010]). D6 furthermore comprises a general disclosure of therapeutical compositions comprising a pharmacologically acceptable amount of donepezil hydrochloride in the form of a polymorph and a pharmacologically acceptable carrier (page 27, last paragraph - page 28, first paragraph and claim 82). Since D6 is also concerned with the stability of donepezil hydrochloride in terms of the amount of

impurity generated on storage (see pages 1 and 2 and the stability tests on pages 67-69), the technical problem addressed is not different to that addressed in D2.

3.6 The respondent has argued in writing that D2, in addition to not disclosing compositions "having a water content of 3 to 10 % by weight", contains no clear and unambiguous disclosure of donepezil hydrochloride in *hydrate* form as required by claim 1. On other hand, the patent itself refers to the polymorphic forms according to D6 as preferred forms of donepezil hydrochloride according to the patent (paragraph [0010]) and the respondent accepted during oral proceedings before the Board that the composition of claim 1 of the main request differs from the disclosure in D6 in that it specifies a water content of 3 to 10% by weight. Although in written proceedings the respondent had added that D6 does not disclose a *specific* pharmaceutical composition comprising donepezil hydrochloride, this cannot serve as a difference with respect to claim 1 of the main request, especially in view of the general disclosure in D6 of a therapeutical compositions comprising a pharmacologically acceptable amount of donepezil hydrochloride in the form of a polymorph and a pharmacologically acceptable carrier (page 27, last paragraph - page 28, first paragraph and claim 82). There is no reason to interpret "pharmaceutically acceptable carrier" in the context of D6 as being any different from "excipients" according to claim 1 of the main request.

3.7 On that basis, the Board considers document D6 as the closest prior art.

3.8 As noted above, the composition of claim 1 of the main request differs from the generic disclosure in D6 in that it specifies a water content of 3 to 10% by weight.

4. *Technical problem solved*

4.1 The problem to be solved according to the application as filed is to avoid a conversion of the polymorphic form of donepezil hydrochloride when processing it to the desired solid composition, and stabilising said polymorphic form during the shelf-life of said composition (page 2, final paragraph; page 3, first paragraph).

4.2 In order to formulate the objective technical problem effectively solved by the claimed subject-matter, it must be determined whether it provides by virtue of the distinguishing features over the closest prior art the alleged technical effects or advantages. It is established case law that alleged effects or advantages which are neither credible nor supported by sufficient evidence cannot be taken into consideration in determining the objective technical problem (Case Law, *supra*, I.D.4.2).

4.3 To this end, the evidence on file must be examined to determine whether the alleged effect with respect to the closest prior art (avoiding the conversion of the polymorphic form of donepezil hydrochloride during preparation of a solid composition and during the shelf-life thereof) has been substantiated.

4.4 According to the respondent, the technical effect is demonstrated by example 4 (paragraphs [0072] to [0078]) and figure 1 of the patent whereby the stability of the

polymorphic form in tablets comprising donepezil hydrochloride hydrate and having a water content of 5.5 % by weight was confirmed by XRPD analysis.

4.5 Example 4(b) of the patent (paragraphs [0077] and [0078]) describes the stability testing of the tablets, the results of which were displayed in the X-ray pattern of figure 1. Here, the upper diffraction pattern corresponds to the tablets according to the invention prepared by water granulation (presumably measured directly after preparation), the middle pattern corresponds to the same tablets after storing for 30 days at 50°C, and the lower pattern corresponds to donepezil hydrochloride hydrate (without excipients). It is concluded that the absence of other diffraction peaks in the middle pattern indicates that there are no other forms of donepezil hydrochloride present, i.e. that the polymorphic form in the (aged) composition of the invention has remained unchanged (paragraph [0078]).

4.6 Although several separate objections have been raised by the appellants against the validity of the tests of the patent, the critical issue in the view of the Board is that said tests do not provide a comparison with the closest prior art D6, which would be necessary to prove that the alleged effect originates in the distinguishing feature of the invention over the closest prior art, i.e. in the specific water content of the tablet composition. Thus it would need to be shown not only that the alleged effect is present in respect of the claimed composition, but also that an improvement is present with respect to compositions having a water content falling outside of the claimed range. Furthermore, despite the objection as to the lack of comparative data being raised as early as the

filing of the notices of oppositions, the respondent has not filed any evidence which attempts to overcome this shortcoming. Furthermore, there is no evidence on file that the alleged problem even existed for the compositions of the prior art, such as the Aricept® tablets (see for example, D21).

4.7 It follows that the alleged effect of avoiding the conversion of the polymorphic form of donepezil hydrochloride during preparation of a solid composition and during the shelf-life thereof is not supported by any evidence and therefore cannot be taken into consideration in formulating the objective technical problem. As a consequence of this, the other objections raised by the appellants in relation to the validity of the tests in the patent do not need to be addressed by the Board.

4.8 It follows that the objective technical problem underlying claim 1 of the main request is the provision of a further pharmaceutical composition comprising a hydrate of donepezil hydrochloride.

5. *Obviousness*

5.1 The question remaining is whether the skilled person, starting at the solid pharmaceutical compositions of donepezil hydrochloride hydrate disclosed in the closest prior art D6, would have arrived at the subject-matter of claim 1 of the main request in order to solve the problem posed.

5.2 In order to answer this question, it is relevant to note that, when the technical problem is simply that of providing a further composition of matter, any feature or combination of features already conventional for

that sort of composition of matter represents an equally suggested or obvious solution to the posed problem. The Boards of Appeal have repeatedly established that the simple act of arbitrarily selecting one among equally obvious alternative variations is devoid of any inventive character (Case Law, *supra*, I.D.9.18.7).

5.3 In the present case, the respondent has not presented any evidence that the claimed water content of 3-10 % by weight is anything but conventional. On the contrary, several appellants have attempted to calculate the water content achieved by preparing the solid compositions of example 1 of D2 in a conventional manner by using the standard minimum and maximum water contents of the excipients used taken from D18 and D19. Appellant-opponent 1 concluded that preparing the solid pharmaceutical composition of example 1 of D2 led to a composition having a water content ranging from a minimum of 4.02 % by weight to a maximum of 6.15 % by weight (letter of 1 May 2013, points 46-49); similarly appellant-opponent 4 calculated the maximum and minimum water content thereof to be 3.44 wt% and 6.1 wt% respectively (page 6, points 3.42 and 3.43 of the letter of 30 April 2013); and appellant-opponent 6 provided 4.30 wt% and 6.90 wt% as the corresponding minimum and maximum values (page 11, tables 1 and 2 of the letter of 24 April 2013). Furthermore, D22 and D25, filed by appellant-opponent 4 comprise calculations of the water content of the commercially available Aricept® tablets (which comprise the same excipients as the composition of example 4 of the patent and example 2 of D2) manufactured both before the priority date (D22: 5.5 wt.% and D25: 5.7 wt%) and after the priority date (D22: 4.9 wt% and D25: 5.7 wt%); and a further analysis of the Aricept® tablets provided by appellant-opponent 8

calculated the water content as 4.6 wt% (D46). These values generally fall in the middle of the claimed range, and are very close to the calculated water content of 5.5 % provided for the tablets prepared according to the patent (paragraph [0076]). Consequently, the claimed water content range of 3 to 10 % by weight can only be seen as an arbitrary and therefore obvious selection within which the water content conventionally achieved for the compositions of the prior art falls.

5.4 It follows from the foregoing that claim 1 of the main request does not involve an inventive step.

Auxiliary requests - inventive step

6. *First auxiliary request - inventive step of claim 1*

6.1 Independent claim 1 of the first auxiliary request differs from that of the main request by the limitation of the donepezil hydrochloride hydrate to the monohydrate of polymorphic form I. As acknowledged by the respondent, the closest prior art D6 discloses said form, meaning that claim 1 does not comprise any further technical features distinguishing it therefrom (see point 3.5, above). The conclusion with respect to inventive step consequently remains the same as for claim 1 of the main request (see point 5, above).

7. *Second auxiliary request - inventive step of claim 1*

7.1 Independent claim 1 of the second auxiliary request differs from that of the first auxiliary request by the limitation of the water content of the composition to the narrower range of "4 to 7 % by weight". The arguments provided above with respect to the lack of an

effect (points 4.6 and 4.7) and of the arbitrary and conventional nature of the wider range (point 5.3) are equally valid for the narrower range, and consequently the conclusion with respect to inventive step remains the same as for claim 1 of the main request (see point 5, above).

8. *Third auxiliary request - inventive step of claim 1*

8.1 Independent claim 1 of the third auxiliary request differs from that of the second auxiliary request in that it is specified that the solid pharmaceutical composition "is in the form of a tablet". Since tablets are disclosed in D6 as one of the dosage forms which may be employed (D6, page 29, penultimate paragraph), claim 1 does not comprise any further technical features distinguishing it from the closest prior art D6, and the conclusion with respect to inventive step remains the same as for claim 1 of the main request (see point 5, above).

9. *Fourth auxiliary request - inventive step of claim 1*

9.1 Independent claim 1 of the fourth auxiliary request differs from that of the third auxiliary request in that it is further specified that "the excipients include at least one diluent selected from microcrystalline cellulose and lactose monohydrate". While this feature may formally constitute a further distinguishing feature with respect to the generic disclosure in D6, there is no evidence of possible effects or advantages related to it. Therefore the technical problem remains the same as above (see point 4.8).

9.2 The specified excipients are commonly used in the field as shown by the compositions provided in the examples of D2 (page 15 and following) and by the composition of the commercially available Aricept® tablets (see D21). The skilled person starting at the disclosure of D6 and wishing to provide further pharmaceutical compositions comprising a hydrate of donepezil hydrochloride would use without any inventive activity excipients commonly known in the art for the same kind of compositions of same active agent. It follows that also claim 1 of the fourth auxiliary request does not involve an inventive step.

10. *Fifth auxiliary request - inventive step of claim 1*

10.1 Independent claim 1 of the fifth auxiliary request differs from that of the third auxiliary request in that it further specifies a condition on the migration of water from the excipients to the donepezil hydrochloride or vice versa (which is prevented), as well as the means for fulfilling that condition in terms of the definition of two kinds of excipients (according to their quantities) and of the specific water contents of the various ingredients (see point VI, above).

10.2 However, there is no evidence on file that the specific choice of the excipient quantities and of the water contents has indeed an impact on the migration of water, nor that any of the added features (including the prevention of water migration) affects in any way the stability of the composition or provides any further advantage. Thus, there is no further effect which can be taken into account in the formulation of the technical problem, which remains the same as for the main request (see point 4.8). It follows that the

added features can only be seen as an arbitrary selection of a multitude of possibilities available to the skilled person wishing to provide a solution to the problem of providing a further pharmaceutical composition comprising a hydrate of donepezil hydrochloride. Consequently, also claim 1 of the fifth auxiliary request does not involve an inventive step.

11. *Sixth auxiliary request - inventive step of claim 1*

11.1 Independent claim 1 of the sixth auxiliary request differs from that of the fifth auxiliary request in that the excipients of the two kinds are specified and chosen from two lists, and the difference in water content of the various ingredients is further limited (see point VI, above).

11.2 Also in this case, there is no evidence that the added features affect in any way the stability of the composition, nor that they provide any further advantage. It follows that the problem remains the same as for the main request (see point 4.8). The added features are not only arbitrary selections, but they are known at least from D2 (see example 1 of D2 comprising 168 mg of lactose monohydrate at 60 % by weight and 8.4 mg of hydroxypropylcellulose at 3 % by weight). For these reasons, in addition to those provided for the fifth auxiliary request, claim 1 of the sixth auxiliary request does not involve an inventive step.

12. *Seventh auxiliary request - inventive step of claim 1*

12.1 Claim 1 of the seventh auxiliary request differs from that of the third auxiliary request in that it is further specified that the donepezil hydrochloride

monohydrate of polymorphic form I "has an average particle size of 5 to 300 µm" and the excipients "have a particle size of D90<500 µm".

12.2 Also in this case, there is no evidence that the added features affect in any way the stability of the composition, nor that they provide any further advantage. It follows that the problem remains the same as for the main request (see point 4.8). The added features are not only arbitrary selections, but they are common in the art, as shown e.g. by documents D54 and D19. Indeed, D54 comprises a general disclosure of *inter alia* particle size of drug substances in pharmaceutical dosage forms, and teaches that in general coarse material should be ground to a preferable range of from 10 to 40 µm (paragraph bridging pages 5 and 6), a range which falls within the range present in the claim. Furthermore, D19 discloses that the pharmaceutical excipients used according to example 4 of the patent (and example 1 of D2) are conventionally supplied in particle sizes below the claimed upper limit of 500 µm (see D19, page 256, table II for lactose monohydrate; page 85, table I for microcrystalline cellulose; page 485, section 10, "Typical Properties", "Particle size distribution" for corn starch; and page 224, section 10, "Typical Properties", "Particle size distribution" for hydroxypropyl cellulose). It follows that the conventional nature of the particle sizes provided in the claim cannot form the basis for acknowledging inventive step, and the same conclusions with respect to inventive step apply as for claim 1 of the third auxiliary request.

13. *Eighth auxiliary request - inventive step of claim 1*

13.1 Independent claim 1 of the eighth auxiliary request differs from that of the third auxiliary request by the further limitation of the water content of the composition to "5 to 6 % by weight". Although more limited with respect to the range of 4-7 % by weight, the claimed range of 5-6 % by weight does not provide a specific effect or advantage and merely closes in more on the conventional range represented by the water content achieved by the appellants in preparing the composition of example 1 of D2, as well as the water content of the commercially available Aricept® tablets (see point 5.3, above). Consequently, the same conclusions in respect of inventive step apply as for claim 1 of the main request.

14. *Ninth auxiliary request - inventive step of claim 1*

14.1 In the ninth auxiliary requests all product claims have been deleted and independent claim 1 is directed to a process for the preparation of a solid pharmaceutical composition (which is defined as the composition of claim 1 of the third auxiliary request with the exception that the water content remains in the range of 3 to 10 % by weight), said process being defined by a number of process steps including in particular (i) granulating a mixture of excipients using water as granulation liquid to give a granulate, (ii) adding donepezil hydrochloride and excipients to the granulate to give a compression mixture, (iii) compressing the compression mixture to the desired form (see point VI, above).

14.2 The appealed decision did not deal with the inventive step of the process claims separately from the

inventive step of the product claims. The same applies largely to the arguments of the parties. The respondent, in particular, centered the inventive step argumentation on the improved stability of the obtained product, which was claimed also as a result of the process for preparation of the product. In addition, the respondent referred to the claimed process steps as being not conventional.

14.3 It has already been concluded that the alleged effect of avoiding the conversion of the polymorphic form of donepezil hydrochloride during preparation of a solid composition and during the shelf-life is not supported by evidence in the patent due to the lack of comparative data (point 5.3, above). This equally applies to the product claims and to the process claims, as there is no evidence that by performing specific process steps an improvement in stability is obtained.

14.4 It remains to be analysed whether the argument that the process is not a conventional one can be given any weight in the analysis of inventive step. Firstly, it is to be noted that, according to the description of the patent, the process for preparing the composition according to the invention can be carried out as a granulation process or a direct compression process (paragraph [0035]). Two separate wet granulation processes are described, the first corresponding to the presently claimed process in which the donepezil hydrochloride is added after granulation, and the second in which the donepezil hydrochloride is included in the granulation mixture (paragraphs [0036]-[0039]). Both granulation processes are disclosed as preferred embodiments, no preference is given to one over the other and neither is presented as a non conventional

process. As to whether the claimed granulation process can be considered as conventional in view of the prior art, D53 provides the teaching that the subsequent addition of an active agent to a granulated mixture is something which the skilled person would contemplate, particular when the substance may be sensitive to wet granulation (D53, page 317, 4.5.2, points 2 and 3).

14.5 As the argument that the process is not a conventional one cannot be followed by the Board, there is nothing more in the arguments of the respondent which needs to be taken into account and it must be concluded that also the subject-matter of claim 1 of the ninth auxiliary request does not involve an inventive step.

15. *Tenth auxiliary request - inventive step of claim 1*

15.1 Independent claim 1 of the tenth auxiliary request differs from that of the ninth auxiliary request by the further specification "wherein the temperature of the mixture and of the granulate does not exceed 50°C during the granulation step and wherein the water content of the granulate is 0.5 to 2.5 % determined as loss on drying at 85°C, 20 minutes".

15.2 Similarly to the ninth auxiliary request, the arguments of the respondent on inventive step of claim 1 of the tenth auxiliary request related to improved stability and to the choice of non conventional features which are not derivable from the available prior art. However, there is no evidence on file that the added features cause any effect or advantage, nor that they are anything but arbitrary choices of conventional operating conditions.

15.3 With respect to the temperature feature, it is not credible that the temperature of the granulation step has any influence on the stability of the active agent, which is absent during the granulation itself. Moreover, D53 discloses a specific fluidised bed granulation process ("Wirbelschichtgranulierung", page 297-298, point 4.4.5.1) in which the process operates at 40-80 °C, indicating therefore that a temperature of 40°C is a conventional one.

15.4 As to the feature that the water content of the granulate is 0.5 to 2.5 % determined as loss on drying at 85°C, 20 minutes, there is nothing on file showing that this is anything other than an arbitrary selection. In any case, the process must result in a product having a water content of 3 to 10 % by weight as claimed, which will place certain limitations on the extent to which the granulated product can be dried, while still resulting in the solid composition according to the claim. Furthermore, in view of D12 (page 341, last paragraph) drying of a wet granulate to zero moisture is not a conventional step in the art, implying that it is standard practice for some moisture to remain. It follows that this feature is equally an arbitrary and conventional choice.

15.5 Also in this case with no further arguments on the side of the respondent, there is nothing more which needs to be taken into account with regard to inventive step with the consequence that also the subject-matter of claim 1 of the tenth auxiliary request does not involve an inventive step.

Conclusion

16. Since none of the requests on file meets the requirements of Article 56 EPC, the patent is to be revoked and the Board does not need to decide on any other issue.

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:

S. Fabiani J. Riolo

Decision electronically authenticated