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Title of invention:
THERAPEUTIC FORMULATION FOR ADMINISTERING TOLTERODINE WITH CONTROLLED RELEASE

Patent Proprietor:
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Relevant legal provisions:
EPC Art. 56
RPBA Art. 12, 13

Keyword:
Late-filed documents
Inventive step - technical prejudice in the art (no)
Late-filed auxiliary requests - admitted (yes)

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Case Number: T 1478/13 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 16 April 2015

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 25 April 2013 revoking European patent No. 1039882 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Semino
P. Schmitz

Summary of Facts and Submissions

I. The appeal of the patent proprietor (appellant) lies from the decision of the opposition division announced at oral proceedings on 24 January 2013 to revoke European patent 1 039 882.

II. The granted patent comprised 13 claims and included two independent claims directed to the use of tolterodine or related compounds in the manufacture of a medicament for the treatment of unstable or overactive urinary bladder and to a pharmaceutical oral controlled release formulation containing tolterodine or related compounds.

III. Thirteen notices of opposition were filed in which revocation of the patent in its entirety was requested.

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

OD5: Hills et al., Drugs, volume 55(6), 1998, pages 813-820
OD11: Garcia et al., Pharm. Acta Helv., volume 53(3/4), 1978, pages 99-109
OD14: Nilsson et al., Neurology and Urodynamics, volume 16, 1997, pages 533-542
OD15: Van Kerrebroeck et al., Urology, volume 57(3), 2001, pages 414-421
OD16: Nilverbrant et al., Life Sciences, volume 60(13/14), 1997, pages 1129-1136
OD17: Brynne et al., Int. J. Clin. Pharmacol. & Ther., volume 35(7), 1997, pages 287-295
OD21: Lordi, "Sustained Release Dosage forms", chapter 14 in Lachman et al., "The theory and practice of industrial pharmacy", 1986, pages 430-456

OD22: Affidavit of Paul Abrams dated 25 March 2010
OD23: McKenny et al., JAMA, volume 271(9), 1994, pages 672-677
OD27: Lund, "The Pharmaceutical Codex", The Pharmaceutical Press, 1994, pages 208-214, 248-250
OD37: Appell, Urology, volume 50(supplement 6A), 1997, pages 90-96
OD45: WO-A-95/25506
OD46: WO-A-96/29992
OD47: Skelly et al., J. Controlled Release, volume 14, 1990, pages 95-106
OD48: Stahl et al., Neurology & Urodynamics, volume 14, 1995, pages 647-655
OD50: Robinson and Lee, "Controlled Drug Delivery - Fundamentals and Applications", 2nd edition, Marcel Dekker Inc., 1987, pages 296-297 and 323-325
OD68: Affidavit of David Scholfield dated 16 November 2012 including Exhibits DS1, DS2 and DS3

V. The decision was based on two sets of claims filed during oral proceedings as main request (denoted MR3 according to the minutes, corresponding to Annex III attached thereto) and first auxiliary request (Annex IV attached to said minutes).

Independent claims 1 and 3 of the main request read as follows:

"1. Use of tolterodine, or a pharmaceutically acceptable salt thereof, for the manufacture of a therapeutical formulation for treating unstable or overactive urinary bladder, which formulation is a capsule or tablet for oral administration once daily and provides controlled release of tolterodine, or a pharmaceutically acceptable salt thereof, for at least 24 hours such that a substantially constant serum level

of the active moiety or moieties is maintained for at least said 24 hours, such that the controlled release formulation provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval.

3. A pharmaceutical oral controlled release formulation which is a capsule or tablet for oral administration once daily, containing tolterodine, or a pharmaceutically acceptable salt thereof, which formulation when administered to a patient provides controlled release of tolterodine, or a pharmaceutically acceptable salt thereof, for at least 24 hours such that a substantially constant serum level of the active moiety or moieties is maintained for at least said 24 hours, whereby it provides a mean fluctuation index of said serum level of active moiety or moieties that is not higher than 2.0, said fluctuation index, FI, being defined as FI = (Cmax - Cmin)/AUCτ/τ, wherein Cmax and Cmin are the maximum and minimum concentrations, respectively, of active moiety or moieties, AUCτ is the area under the serum concentration profile, and τ is the length of the dosage interval."

The corresponding independent claims of the first auxiliary request differed from those of the main request by the indication that the capsule or tablet contained a 4 mg dosage of tolterodine.

VI. The decision of the opposition division, as far as relevant to the present decision, can be summarised as follows:

a) The subject-matter of claim 1 of the main request differed from the disclosure of document OD5, which was the closest prior art, by the definition of an oral controlled release (hereinafter: CR) formulation of tolterodine with a specific pharmacokinetic profile for once daily administration, while OD5 disclosed an immediate release (hereinafter: IR) oral formulation thereof. The problem solved was the provision of a composition comprising tolterodine having reduced incidence of side effects, such as dry mouth, while maintaining the desired effect on the bladder. Reformulation of this problem to reflect a superior efficacy was not permissible, as such a reformulation, independently of the relevance of post-published evidence OD15, would go against the teaching and evidence provided by the original application. The provision of a CR formulation was obvious in view of document OD5, which indicated that dry mouth occurred mainly around serum peak concentration of tolterodine, in combination with the general knowledge represented by several prior art documents according to which it was known that the incidence and intensity of side effects might be reduced when peak serum concentration was decreased by using CR formulations. Moreover, the selection of the specific FI value was arbitrary and therefore obvious. Contrary to the view of the patent proprietor, none of the indicated four barriers would have prevented the person skilled in the art from formulating tolterodine in CR

form. In view of that the formulation of claim 1 of the main request was not inventive.

b) The limitation in the first auxiliary request was not suitable for overcoming the inventive step objection and introduced a feature which was never part of the claims, so that it took the opponents by surprise. On that basis the first auxiliary request was not admitted into the proceedings.

VII. The appellant lodged an appeal against that decision. With the statement setting out the grounds of appeal dated 3 September 2013, the appellant filed 15 sets of claims as main request and first to fourteenth auxiliary requests, and submitted the following evidence:

OD90: Affidavit of Philip van Kerrebroeck dated 21 August 2013
OD90A: Drake et al., Drug safety, volume 19(1), 1998, pages 45-55
OD90B: Approval letter for Ditropan XL NAD 20-897, December 1998
OD90C: Jünemann et al., Urologia Internationalis, volume 77, 2006, pages 334-339
OD90D: Staskin et al., Journal of Urology, volume 178, 2007, pages 978-984
OD91: Extract from Cambridge dictionaries online: "maintain"
OD92: Extract from "The Oxford English Dictionary", Clarendon Press, volume IX, 1989, pages 223-226: "maintain"
OD93: Pharmaceutical Approvals Monthly, April 1999, pages 26-30
OD94: Tannergren et al., Molecular Pharmaceutics, volume 6(1), 2009, pages 60-73

With the letter of 3 December 2013, the appellant submitted the following evidence:

OD95: Affidavit of David Scholfield dated 29 November 2013
OD95A: Extract from "Final report of the trial 98-TOCR-007", 13 December 1999, pages 1 and 44-47

With the letter of 13 February 2015 the appellant filed the following evidence:

OD102: Extract from "Physicians' Desk Reference", Medical Economics Data Production Company, 1995, page 1259

With the same letter the appellant filed 7 set of claims as main request and first to sixth auxiliary requests, to replace those on file. The main request and the first, second and third auxiliary requests were identical to the corresponding requests filed with the statement setting out the grounds of appeal, while the newly filed fourth, fifth and sixth auxiliary requests corresponded to the eighth, ninth and tenth auxiliary request thereof respectively.

The main request was identical to that upon which the decision of the opposition division was based.

Claims 1 and 3 of the first auxiliary request corresponded to those of the main request with a bracketed specification in respect of the mean fluctuation index reading "(for n being at least 30 and n is the number of patients)".

Claims 1 and 3 of the second auxiliary request corresponded to those of the main request wherein a dose of tolterodine of 4 mg was specified.

Claims 1 and 3 of the third auxiliary request comprised the features added to the corresponding claims of both the first and second auxiliary requests, while the fourth to sixth auxiliary requests differed from the first to third auxiliary requests respectively by deletion of the use claims.

VIII. With the replies to the statement of grounds, the opponents (respondents) submitted the following evidence:

respondent-opponent 13:
OD96: Novara et al., European Urology, volume 54, 2008, pages 740-764.
OD97: "Anticholinergics for overactive bladder: Evidence, Clinical Issues and Comparisons", Rx Files Newsletter, March 2008.
OD98: Synopsis of OROS clinical trial, pages 1 to 7

respondent-opponent 2:
OD99: FDA Approved label for "Detrol tolterodine tartrate tablets", Pharmacia & Upjohn, March 1998.

respondent-opponent 9:
OD100: EP-A-2 153 825
OD101: WO-A-00/27364

With letter of 6 March 2015 respondent-opponent 2 submitted a decision of the Registrar of Patents, Designs and Trademarks of Israel (OD103) in opposition proceedings to patent application 136294.

IX. In a communication sent in preparation of oral proceedings, the Board addressed *inter alia* inventive step with respect to the product claims of the main request. In particular, the choice of OD5 as closest prior art was accepted, and doubts were expressed as to whether the alleged "barriers preventing modification of IR tolterodine to CR tolterodine" would have discouraged the skilled person from providing a CR formulation thereof. Furthermore, the Board expressed doubts as to whether the dosage feature "4mg", added to some of the auxiliary requests, could serve as a feature upon which inventive step could be based.

X. Oral proceedings were held on 16 April 2015.

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

Admittance of documents filed in appeal

a) While it was true that document OD102 was filed after oral proceedings had been arranged, it was a highly relevant document reinforcing the arguments with respect to novelty, it was not difficult to understand and it was filed more than 2 months before the oral proceedings and in reply to the summons. Consequently, it should be admitted into the proceedings.

b) OD98 submitted by opponent-respondent 13 should not be admitted into the proceedings as the publication date thereof was unknown.

Main request - inventive step

c) The difference between the subject-matter of claim 3 of the main request and the disclosure of OD5, taken as the closest prior art, was that the former provided a CR formulation of tolterodine with a specific pharmacokinetic profile defined by the mean fluctuation index, for once daily administration. The effects of the difference were a reduced incidence of side effects such as dry mouth, and the enhancement of the desired effect on the bladder. These effects were demonstrated by the evidence provided in the patent (example 1 and figure 3) and the post-published clinical study OD15 (page 419, lines 11-13), supported by the affidavit OD90.

d) The data provided by OD15 could be used as evidence for said effects since, as demonstrated in the affidavit OD68, the extended-release capsule formulation referred to in OD15 was almost identical to the CR formulation described in example 1 of the patent. The objective technical problem was to provide a composition comprising tolterodine (or a pharmaceutically effective salt thereof) which had a reduced incidence of side effects, such as dry mouth, while enhancing the desired effect on the bladder. The refusal of the opposition division to allow said (re)formulation of the problem in view of the perception that it would go against the whole teaching of the original application, was incorrect.

e) The solution to said problem, but also to the problem as formulated by the opposition division, i.e. the provision of a composition comprising

tolterodine (or a pharmaceutically effective salt thereof) which had a reduced incidence of side effects, such as dry mouth, while maintaining the desired effect on the bladder, was not obvious in view of the prior art and the evidence provided by the affidavits OD90 and OD22 demonstrating that there were at least four "barriers" which would deter the skilled person from modifying IR tolterodine to arrive at CR tolterodine, namely 1) the lack of incentive to modify IR tolterodine, including concerns about urinary retention, and the already adequate side-effect profile of IR tolterodine, 2) the lack of predictability of the effect on efficacy and side effect profiles, 3) the lack of success of CR oxybutynin in reducing side effects, and 4) the unknown bioavailability of tolterodine from a CR formulation.

f) The proposed solution did not result from the skilled person having found himself in a "one-way-street" situation at the priority date. There were viable alternatives to the use of an oral controlled release formulation such as the use of transdermal or vaginal delivery systems which the skilled person could have investigated in order to solve the posed problem.

g) In view of this, the skilled person wishing to solve said problem would not have modified IR tolterodine to produce CR tolterodine without exercising inventive step.

Auxiliary requests - admittance

h) The auxiliary requests should be admitted since the features added with respect to the main

request were inserted in reaction to the decision and to objections of the respondents. In particular, the "4 mg" dosage feature corresponded to the dosage used in the OD15 study and was intended to overcome the assertion that the technical problem was not solved across the whole scope of the main request. A late-filed challenge in respect of this feature was not justified since the proprietor had attempted to introduce it during opposition proceedings. Furthermore, the feature "(for n being at least 30 and n is the number of patients)" was a precaution in view of an objection of lack of sufficiency which was not followed by the opposition division.

Auxiliary requests - inventive step

i) The arguments concerning the presence of inventive step developed for the main request applied to the product claims of the auxiliary requests. In addition, the dose of 4 mg corresponded to the one for which the successful tests were available.

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

Admittance of documents filed in appeal

a) Documents OD90 - OD95A were late filed and consequently should not be admitted into the proceedings. In particular, the affidavits OD90 and OD95 were not relevant, since they were filed to support an unallowable reformulation of the technical problem, and documents OD90C, OD90D, OD93 and OD95A were published after the effective date of the patent and consequently could not be

used as evidence to support the alleged improved efficacy.

Main request - inventive step

b) The closest prior art was represented by OD5. The difference between the subject-matter of claim 3 of the main request and the disclosure of OD5 was that the former provided a CR formulation of tolterodine with a specific pharmacokinetic profile defined by the mean fluctuation index, for once daily administration, whereas the latter related to an IR formulation of tolterodine. The problem to be solved according to the application as filed was the provision of a composition comprising tolterodine which provided a reduced incidence of side effects, particularly dry mouth, while maintaining the desired effect on the bladder. An enhancement of the efficacy on the bladder could not be acknowledged in view of the results in example 1 of the patent, which showed maintenance of efficacy, and of the differences between the composition tested in the patent and that of OD15, which explained why in one case maintenance of efficacy was obtained, while in the other enhanced efficacy was found. In order to solve the posed problem, the skilled person would immediately consider providing a CR formulation of tolterodine, since based on his general knowledge he would have a reasonable expectation that such a formulation would avoid the creation of the peak serum concentration levels at which, according to OD5, inhibition of stimulated salivation is said to occur, thereby solving the problem of dry mouth associated with said peaks, without loss of efficacy. None of the alleged barriers mentioned

by the appellant constituted a sufficient disincentive for the skilled person to choose the obvious route of developing a CR formulation in order to solve the posed problem. The claimed subject-matter consequently lacked inventive step.

Auxiliary requests - admittance

c) In accordance with Article 12(4) RPBA, the auxiliary requests should not be admitted into the proceedings, since they either included an amendment which was not admitted during first instance proceedings, or they represented requests which could have been presented in the first instance proceedings.

Auxiliary requests - inventive step

d) The arguments developed for lack of inventive step of the main request applied to the product claims of the auxiliary requests.

XIII. The appellant requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request, alternatively on the basis of one of the first to sixth auxiliary requests, all filed with the letter of 13 February 2015.

XIV. The respondents requested that the appeal be dismissed.

Reasons for the Decision

Admittance of documents filed in appeal

1.1 Documents OD90-OD95A were filed by the appellant with the statement of grounds of appeal or shortly

thereafter (OD95 and OD95A) to counter the reasoning on inventive step in the appealed decision, in particular to support the reformulation of the solved problem, to reinforce the existence of barriers against the obviousness of the solution and to strengthen the relevance of the experimental data. Documents OD96, OD97 and OD99-OD101 were filed by the respondents with their replies to the statement of grounds to counter the arguments of the appellant developed therein, namely to show the lack of relevance of the barriers (OD96, OD97 and OD99), or to dispute the decision on novelty of the opposition division (OD100 and OD101), which was in favour of the appellant. All these documents were therefore timely filed by the parties in appeal and can be seen as legitimate reactions to the decision or to the statement of grounds, so that the Board sees no reason under Article 12(4) RPBA not to admit them. On that basis documents OD90-OD97 and OD99-OD101 are admitted into the proceedings.

1.2 As to documents OD98 (whose admittance was contested on the basis of the lack of a publication date) and OD102 (filed by the appellant after oral proceedings had been arranged and relevant for lack of novelty), it is not necessary for the Board to take a decision on their admittance, since the parties did not rely on said documents in their arguments relevant for the decision.

1.3 As to document OD103, it was filed after oral proceedings had been arranged and concerns a decision in opposition proceedings in Israel against a parallel patent. As the document is undoubtedly late filed, it is not known to what extent the proceedings related to the same issues as the current ones and the decision in any case bears no weight on the current one, the Board finds it appropriate to exercise its discretion

according to Article 13 RPBA by not admitting the document into the proceedings.

Main request - inventive step

Closest prior art

2. According to the decision under appeal, the appellant and the respondents, document OD5 represents the closest prior art. The Board sees no reason to choose a different approach.

2.1 OD5 discloses orally administered tolterodine in the context of the treatment of overactive bladder (summary, first sentence; page 815, "Human studies"). Tolterodine is noted as being "as potent as oxybutynin in inhibiting bladder contraction, but much less in inhibiting salivation, suggesting that it may have less propensity to cause dry mouth in clinical use" (summary, second sentence). Despite this, dry mouth still appears to be the most frequent adverse event (see table, page 813). Furthermore, it is disclosed that the "inhibitory effects of tolterodine on stimulated salivation ... were apparent only around the time of peak serum drug concentrations" (page 815, right hand column, second bullet point).

2.2 It is undisputed that the difference between the subject-matter of product claim 3 of the main request and the disclosure of OD5 is that the former provides an oral CR formulation of tolterodine with a specific pharmacokinetic profile defined by the mean FI, for once daily administration, whereas the latter relates to an oral IR formulation of tolterodine.

Problem solved

3. The problem solved by the claimed composition according to the application as filed is the provision of a composition comprising tolterodine which provides a reduced incidence of side effects, particularly dry mouth, while maintaining the desired effect on the bladder (page 3, lines 8-18).

3.1 In view of the evidence presented in OD15, the appellant contends that the problem should be reformulated to include the aspect of enhancing the desired effect on the bladder, i.e. as providing a composition comprising tolterodine which provides a reduced incidence of side effects, particularly dry mouth, while enhancing the desired effect on the bladder.

3.2 While the opposition division in the decision under appeal concluded that said reformulation was unallowable since it would go against the teaching and evidence of the original application, the Board considers that firstly it needs to be established whether the alleged effect of enhanced efficacy with respect to the closest prior art is supported by sufficient evidence, since according to established case law, alleged advantages to which the patent proprietor merely refers, without offering such evidence, cannot be taken into consideration in determining the objective problem underlying the invention.

3.3 The appellant has conceded that the data provided in the patent do not serve as evidence of the alleged effect of increased efficacy, stating that the use of residual urine volumes to measure efficacy was a fairly

rudimentary method for doing so, but also that it was difficult to obtain accurate measurements using ultrasound, the method used according to the patent (see page 18, item k) of the letter of 13 February 2015). Thus the patent does not provide evidence of said effect.

3.4 The appellant on the other hand relies on evidence provided by post-published document OD15 to support the allegation of enhanced effect. This document discloses a clinical trial report according to which an oral CR tolterodine formulation was reported to be 18 % more effective than the corresponding IR formulation in reducing incontinence episodes (page 419, lines 11-12). It is apparent from the affidavit OD68 that the trial referred to in OD15 was conducted by Pharmacia and denoted 98-TOCR-007, an extract from the final report of which was filed as Exhibit DS1 attached to OD68. Exhibit DS2 attached to said affidavit in turn shows that the formulation P902255A01 was used in trial 98-TOCR-007 (table 11.2 on page 47). DS2 sets out the structure and content of the formulation P902255A01 in table 11.7. Finally, exhibit DS3 discloses that said formulation has a mean fluctuation index of 1.5. That this formulation represents the one which was employed in the clinical trial OD15 is thus established and indeed, has not been disputed by any of the respondents.

3.5 Thus, given the evidence provided by OD15, the effect of increased efficacy has been demonstrated for the specific formulation disclosed in exhibit DS2 (table 11.7) which, possessing a mean FI of 1.5, falls within the scope of product claim 3 of the main request.

3.6 The question remains as to whether the evidence provided by OD15 for the single formulation disclosed in DS2 renders it plausible that the effect of increased efficacy is achievable over the whole area presently claimed, in particular in view of the fact that the patent contains data in example 1 which show that the effect on the bladder is maintained (see in particular paragraph [0037]).

3.7 The appellant, particularly according to the affidavit OD68, has conceded that the tolterodine formulation used in OD15 was almost, but not identical to that of example 1 of the patent. However, as noted in particular by respondent-opponent 4 during oral proceedings before the Board, in addition to the apparently minor differences laid out in OD68 (table, point 5), at least one further difference lies in the "overcoat layer", present in the formulation according to exhibit DS2, but lacking in the formulations according to example 1 of the patent. More importantly, the measured mean fluctuation index values is 1.5 for the formulation of exhibit DS2, and 0.68 for that of example 1 of the patent. In the opinion of the Board, and without wishing to speculate on the specific nature of the causative factors (eg. relative amounts of the ingredients, the presence of an overcoat layer, the specifics of the manufacturing process, etc.), the relatively large difference in the mean fluctuation index values of the respective formulations compared to the claimed value of "not higher than 2" is indicative of non-trivial differences in the nature of the respective formulations. Thus the Board cannot accept the statement in OD68 whereby the respective formulations are said to be almost identical, since they differ significantly in the specific parametric

property used to define the tolterodine formulations of the product claims over those of the prior art.

3.8 Given the differences in said formulations and the fact that for the formulation in DS2 an enhancement of the effect has been shown, but for the formulation of example 1 of the patent maintenance of the effect has been found, it is not possible to state that the effect of improved efficacy demonstrated in OD15 arises from the differentiating feature with respect to the closest prior art OD5. It is equally conceivable that the effect arises from the differences in the respective formulations outlined above. In view of this, the data provided by OD15 cannot be accepted as credible evidence that the tolterodine formulation of example 1 of the patent, for which maintenance of the efficacy has been shown in the patent, would also display the effect of enhanced efficacy. Consequently it has not been sufficiently demonstrated that the effect of enhanced efficacy is achievable over the whole area claimed.

3.9 It follows that this effect cannot be used in the formulation of the objective technical problem underlying the invention.

3.10 As far as the effects of reduction of side effects and maintenance of the efficacy on the bladder are concerned, the respondents have not contested that they are achieved by the claimed formulation and the Board has no reason to doubt that it is indeed the case in view of the available evidence (see in particular example 1 in the patent).

3.11 In view of the above considerations, the problem solved is the provision of a composition comprising

tolterodine which provides a reduced incidence of side effects, particularly dry mouth, while maintaining the desired effect on the bladder.

Obviousness

4. The respondents have argued that the skilled person, starting at the disclosure of OD5 and wishing to solve the objective technical problem as set out above, would immediately consider providing an oral CR formulation of tolterodine, as he would have a reasonable expectation that such a formulation would avoid the creation of the peak serum concentration levels at which inhibition of stimulated salivation is said to occur on administration of the IR formulation disclosed in OD5, thereby solving the problem of dry mouth associated with said peaks, without loss of efficacy.

4.1 The position taken by the appellant in defence of inventive step of the claimed subject-matter starting from the objective technical problem as outlined above (section 3.11) is based on the argument that four specific "barriers", or technical prejudices existed in the prior art which would have deterred the skilled person from modifying oral IR tolterodine to produce oral CR tolterodine in order to solve said problem. Said barriers are (1) the lack of incentive to modify IR tolterodine,(2) the lack of predictability of the effect on efficacy and side effect profiles in switching from IR to CR generally, (3) the lack of success of the CR oxybutynin formulation in reducing side effects and (4) the unknown bioavailability of tolterodine from a CR formulation.

4.2 The Board sees no reason to disagree with the opinion of the opposition division expressed in section 2.7.3

of the appealed decision, and shared by the respondents. The closest prior art OD5 discloses that the inhibitory effects of tolterodine on stimulated salivation were apparent only around the time of peak serum drug concentrations (OD5, page 815, right hand column, second bullet point). The skilled person looking for an oral composition comprising tolterodine which provides a reduced incidence of side effects, particularly dry mouth, while maintaining the desired effect on the bladder, would search for a means to lower said peak concentrations. In this regard, the large body of evidence on file indicates that it was generally known that peaks may give rise to side effects which may be reduced by the use of controlled release formulations *(inter alia* OD11, OD27, OD21, OD45, OD46, OD50). OD50, for example, on page 296 under the heading "III. Rationale for controlled release dosage forms", describes "some obvious advantages to the use of controlled release products...", and includes the following statement: "In cases where a constant drug level is desirable, a controlled release dosage form may decrease the drug concentration's fluctuation by (a) reducing the peak blood levels (C_{max}) thus potentially reducing dose-related adverse effects,.." (page 296, point 2 under heading III). The Board is thus left with no doubt that the development of a CR formulation was the method of choice in the art for achieving this.

4.3 While not disputing the contention of the appellant that there were viable alternatives to the use of an oral CR formulation available to the skilled person, such as the use of transdermal or vaginal delivery systems, there is no doubt that the skilled person starting at the *oral* dosage formulation of the closest prior art OD5 would first look to solutions involving

oral delivery forms, of which, as mentioned above, the development of a CR formulation was the method of choice in the art for solving the technical problem in question.

4.4 Furthermore, the parameters related to the specific dosage interval and mean fluctuation index recited in claim 3 are not discussed in OD5. However, rather than being intended as specific ranges defining a particular subset of CR formulations, they merely provide a more precise definition of the term "controlled release" according to the invention. This is confirmed in the patent whereby it is explicitly stated that "substantially constant" with respect to the serum level of the drug means that the release profile of the CR formulation should essentially "not exhibit any peak values", the latter being expressed by reference to the fluctuation index (paragraph [0013]). There is no evidence that said features are anything more than standard descriptors of controlled release formulations in general. Consequently, they do not constitute a basis for acknowledging inventive step.

4.5 It remains to be examined whether the technical prejudices alleged by the appellant have been proven, and if so, the impact thereof on the question of obviousness. Accordingly, each of the so-called "barriers" will be discussed in turn.

(1) the lack of incentive to modify IR tolterodine

4.6 The first barrier is the alleged lack of incentive to modify IR tolterodine in view of the pharmacokinetic and pharmacodynamic studies performed during the development thereof, which indicated a risk of urinary retention, an undesirable side-effect. According to the

affidavit OD90, the skilled urologist would have concluded from said studies that a once daily tolterodine formulation presented a risk that, with subsequent doses, the bladder may become "too" inhibited and result in significant, and potentially harmful urinary retention (point 19). While OD90 (point 14) acknowledges that some of the studies relied upon to arrive at this conclusion (OD17 and OD48) relate to relatively high doses of tolterodine, it also mentions that the same problems were reported even for the lower doses in OD16. The author of OD90 concludes that in his opinion, the risk of urinary retention was a significant disincentive to modify the IR formulation of tolterodine to produce a CR formulation (point 19). Furthermore, he declares to be in agreement (point 20) with the comments of another expert provided in the affidavit OD22 that there was a further disincentive to modify in view of the loss of dose flexibility (point 4), and that IR tolterodine was already perceived as an ideal treatment due to the lack of severe side effects associated with peak serum concentrations of tolterodine (OD22, point 5).

4.7 According to OD16 (table III, page 1135 and the subsequent paragraph), urinary retention was reported in 1 from 65 subjects at a tolterodine dose of 2 mg. Notwithstanding the low occurrence reported, such a result is hardly of any statistical significance. Significant problems with urinary retention arise only at higher, non-therapeutic doses of the drug. Furthermore, according to OD99 (the product label for commercial oral IR tolterodine 2 mg), not only did urinary retention occur less often in patients treated with Detrol 2 mg than in those in the placebo group (see table on the penultimate page), but all urinary related side effects occurred at a lower frequency for

the tolterodine patients than those receiving placebo. The Board notes that in contrast, 39.5% of patients reported dry mouth as an adverse effect compared to 15.9% in the placebo group. It follows that the argument that the skilled person would have been concerned about the incidence of urinary retention to the extent that it would act as disincentive to modify IR tolterodine with a view to reducing side effects such as dry mouth is not convincing to the Board.

4.8 Regarding the alleged disincentive to modify in view of the loss of dose flexibility mentioned in the affidavit OD22 (point 4), the expert expressed therein his recollection of the instructions issued by urologists to patients in 1998. The author of OD90 was in agreement therewith (OD90, point 20). Nevertheless, a mere recollection of dosage regimen instructions from twelve years prior to the date of the affidavit in question cannot be seen to constitute concrete evidence in support of this view. Furthermore, the advice that oral IR tolterodine should be taken in the morning and shortly before sleeping is hardly surprising given the fact that peak serum concentrations were reached shortly after administration: it was desirable that the patient would not have to get out of bed to pass urine at night, and the most efficient way to prevent this was to administer before sleeping, since administration during the night would contradict the desired result. Furthermore, the skilled urologist at the time would have devised the most appropriate dosage regimen within the pharmacokinetic constraints imposed by the oral IR tolterodine available at the time. This cannot be interpreted as evidence that the skilled urologist would not have been interested in an oral CR formulation of tolterodine, as alleged by the appellant. Rather, he simply worked within the

constraints of what was available before the priority date of the patent. This alleged disincentive is consequently considered unconvincing.

4.9 Furthermore, in support of alleged perception before the priority date that IR tolterodine was an ideal treatment (the implication being that the skilled person would have no incentive to improve it), the appellant relies on OD37 in which it is recorded that 17% of patients taking 2 mg tolterodine reported severe dry mouth, and contrasts this with the corresponding reported figure of 60 % for oxybutynin (page 93, figure 5 and last sentence of left column). An inconsistency thus arises in the argumentation of the appellant who contends on the one hand that a single case of urinary retention from 65 patients (according to OD16) serves as a disincentive to modify oral IR tolterodine, while on the other hand, the finding that 17% of patients being administered oral IR tolterodine 2 mg reported severe dry mouth (according to OD16) is not a sufficient incentive for the skilled person to considering improving the formulation. In any case, the Board sees no reason why the skilled person would necessarily accept that the reported level of severe dry mouth caused by IR tolterodine of 17% was ideal and not open to improvement.

(2) the lack of predictability of the effect on efficacy and side effect profiles in switching from IR to CR generally

4.10 The appellant contends that it was well known to the skilled person at the priority date of the patent that an oral CR formulation of a particular active ingredient did not necessarily improve the side effect profile of the active ingredient, and that as a

consequence, he would not have considered this modification. Two documents in particular are cited, the first of which discloses that sustained release niacin was disadvantageous compared to IR niacin (OD23) and the second of which comprises the general statement that "In other instances, controlled-release products may have no significant advantages or they may actually be less effective... than conventional dosage forms of the same drug" (OD47, page 95, middle of right column). The appellant considers the documents cited in the decision of the opposition division (section 2.7.3) as general/theoretical disclosures not directed to a specific drug.

4.11 The Board cannot follow the conclusions of the appellant in this regard, for the reasons set out by some of the respondents. While is is accepted that not *all* CR formulations will provide advantageous effects with respect to the corresponding IR formulation, and there will be an occasional failure such as that demonstrated in OD23, a large number of references have been cited in the present proceedings (*inter alia* OD11, OD27, OD21, OD45, OD46, OD50) according to which controlled release formulations may help to overcome efficacy and side-effect issues. In particular the fact that the use of a CR formulation will result in smoothing out the peaks of the serum concentration (which is the basic information needed to accomplish the choice when addressing the posed problem starting from OD5) is supported by all documents cited and is in agreement with the common general understanding of how CR formulations work. Indeed, in criticising the documents cited by the opposition division in this regard, the appellant acknowledges the generality of the teachings thereof. These documents more accurately represent the general expectations of the person

skilled in the art and the small number of disclosures cited by the appellant in support of his position represent the exception rather than the rule: the general benefits of controlled release formulations are well known in the art. In this context it must be emphasised that the skilled person, in order to be motivated to proceed with a certain measure, does not require absolute certainty as to the success of that measure, rather he requires a reasonable expectation of success. Consequently, the evidence cited by the appellant in this regard is insufficient to demonstrate that the skilled person would not proceed in the modification of oral IR to CR tolterodine with reasonable expectation of success based on the prior art knowledge.

4.12 It follows that the alleged "lack of predictability" cannot represent a disincentive to the skilled person in the sense argued by the appellant.

(3) the lack of success of the CR oxybutynin formulation in reducing side effects

4.13 The appellant refers to the affidavit OD90 (paragraphs 22-25) and *inter alia* OD14, which discloses a clinical comparison of CR with IR oxybutynin, to argue that there was no conclusive evidence of improved tolerability in the former, and that consequently there was no motivation to the skilled person to develop a CR dosage form of tolterodine since he would expect it to act in a similar manner.

4.14 The Board cannot follow the arguments of the appellant, even if the position with respect to the lack an improvement in tolerability of CR over IR oxybutynin were to be accepted. As noted by the respondents, in

particular respondent-opponent 2 (page 9 of the letter of 9 January 2014), the person skilled in the art was aware *inter alia* from the disclosure of the closest prior art OD5 that the affinity of tolterodine to the receptors of the salivary glands was eight times smaller than that of oxybutynin. The distinction is neatly illustrated in OD5, figure 1, which shows that the intravenous dose of oxybutynin required to inhibit acetylcholine-induced bladder contraction by 50% (ID_{50}) is *higher* than that required to inhibit electrically stimulated salivation. From this the skilled person understands that the therapeutic dose of oxybutynin will overlap with the dose which causes salivary inhibition. In contrast, the opposite is true for tolterodine, which shows a much greater specificity for the receptors of the bladder over those of the salivary glands (still figure 1 of OD5). Thus the skilled person knew that the therapeutic window for tolterodine (the range from the therapeutic to "toxic" dose) was much wider than that for oxybutynin and thus, even though CR oxybutynin may not have reduced the number of instances of dry mouth with respect to IR oxybutynin, the skilled person would have understood why, and consequently, in contrast to that alleged by the appellant, would not necessarily have expected the same difficulty in considering a switch from IR to CR tolterodine.

(4) the unknown bioavailability of tolterodine from a controlled release formulation

4.15 Citing OD17 as evidence that IR tolterodine is absorbed rapidly in the small intestine, the appellant argues that at the priority date of the patent, nothing was known from the prior art about how efficiently tolterodine would be absorbed from the lower GI tract, where the vast majority of drug release would take

place for a CR formulation, and that consequently, it would be impossible for the skilled person to predict whether sufficient tolterodine would be absorbed to result in an efficacious formulation. The disclosure of an oral CR formulation of oxybutynin in OD14 would provide the skilled person with no guidance in developing CR tolterodine.

4.16 The Board cannot follow the position of the appellant in this regard. Firstly, the alleged difficulty in *predicting* the lower GI tract bioavailability of tolterodine does not equate to a disincentive for the skilled person, i.e. a credible teaching that tolterodine was unlikely to possess the requisite bioavailability. In this respect OD17 merely disclosed that IR tolterodine was absorbed from the small intestine, which is to be expected given the immediate release profile of the formulation and the expected residency time thereof in the small intestine, but provides no information with respect to its bioavailability in the lower GI tract. On the contrary, the fact that it was known at the priority date of the patent that oxybutynin was successfully adapted to a controlled release formulation (see OD14) despite a lack of data regarding its absorption from the lower GI tract, can only be seen as providing the skilled person with a reasonable expectation of similar results in adapting oral IR to CR tolterodine.

Conclusions

4.17 According to established case law, a high standard of proof is required to demonstrate that a known prejudice really existed in the art. In the foregoing it has been demonstrated that the arguments of the appellant in

respect of the so-called "barriers" have failed to reach this standard.

4.18 Since the presence of a technical prejudice in the art which would deter the skilled person from modifying oral IR to produce oral CR tolterodine with a view to solving the objective problem has not been proven, the conclusions reached above (points 4.3-4.5) remain valid.

4.19 It follows that claim 3 of the main request does not involve an inventive step.

Auxiliary requests - admittance

5. All auxiliary requests were originally submitted with the statement setting out the grounds of appeal, and were subsequently renumbered with the letter of 13 February 2015 after deletion of some originally filed claim requests. Thus according to Article 12(1) RPBA, the auxiliary requests form part of the basis for appeal proceedings.

5.1 However, the respondents considered that they should not be admitted under Article 12(4) RPBA, which gives the Board the discretion to hold inadmissible requests which could have been presented or were not admitted in the first instance proceedings.

5.2 The amendment in claims 1 and 3 of the first auxiliary request (the bracketed specification in respect of the mean fluctuation index reading "for n being at least 30 and n is the number of patients") was introduced to overcome an objection with respect to sufficiency of disclosure which was decided in favour of the appellant in opposition proceedings. While it may be true that

this request could have been filed during first instance proceedings, there was no need to do that at that stage. Consequently the Board considers it appropriate to admit the first auxiliary request into the proceedings.

5.3 Claims 1 and 3 of the second auxiliary request correspond to those of the main request wherein a dose of tolterodine of 4 mg has been specified. The appellant had introduced the 4 mg dosage feature in an auxiliary request filed at oral proceedings before the opposition division which was not admitted, as it was late-filed, was not suitable for overcoming the inventive step objections, and introduced a feature which was never part of the claims, thus taking the opponents by surprise (see point VI.b), above).

5.4 While the Board sees no reason to doubt that the opposition division exercised its discretion using the correct criteria, the discretion of the Board can be exercised independently, in accordance with Article 12(4) RPBA.

5.5 The second auxiliary request introduces a feature which represents a genuine attempt on the part of the appellant to overcome the critical objection of lack of inventive step and was filed at the beginning of the appeal proceedings, so as to give full opportunity to the respondents to take position on it. On that basis the Board considers it appropriate to admit the second auxiliary request into the proceedings.

5.6 The same holds for the third auxiliary request, which includes the amendments of the first and second auxiliary requests, and for the fourth to sixth auxiliary requests, which are limited to product

claims, which are identical to those of the previous requests.

5.7 It is therefore concluded that the first to sixth auxiliary requests are admitted into the proceedings.

Auxiliary requests - inventive step

6. Claim 3 of the first auxiliary request differs from that of the main request by the added feature "(for n being at least 30 and n is the number of patients)". This feature was introduced by the appellant to overcome an objection raised by the respondents in respect of sufficiency of disclosure. The issue with respect to inventive step remains the same as that for the main request and, consequently, the same reasoning and the same conclusion apply (points 2 to 4, above).

6.1 Claim 3 of the second auxiliary request differs from that of the main request by the specification of a dose of tolterodine of 4 mg, which feature was introduced to overcome the objection that the objective problem was not solved over the whole scope of the claim. The conclusions reached for claim 3 of the main request in respect of inventive step are equally valid for the specific dosage of 4 mg, as it is the daily dosage indicated in OD5 (see table on page 813) and it is tested both in the patent in suit (see example 1) and in OD15, so that the whole reasoning (identification of the closest prior art, formulation of the problem and analysis of obviousness, see points 2 to 4 above) remains the same with the consequence that claim 3 of the second auxiliary request does not involve an inventive step.

6.2 Claim 3 of the third auxiliary request differs from that of the main request by the introduction of the features added to claim 3 of both the first and second auxiliary requests. Thus the conclusion reached in respect of those requests also applies.

6.3 The product claims of the fourth, fifth and sixth auxiliary requests are identical to those of the first, second and third auxiliary requests respectively, so that the conclusions in respect of inventive step apply unchanged.

Conclusions

7. Since none of the requests meets the requirements of Article 56 EPC, the appeal is to be dismissed and there is no need for the Board to decide on any other issue.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated