FEDERAL PATENT COURT

ON BEHALF OF THE PEOPLE

DECISION

Announced on
November 13, 2012

3 Ni 43/10 (EP)
conjoined with
3 Ni 24/11 (EU) and
3 Ni 25/11 (EU)
(Court Reference)

In the patent nullity case

concerning European patent 0 907 364
(DE 697 14 739)

the 3rd Senate (nullity senate) of the Federal Patent Court held, based on the oral proceedings of November 13, 2012 with the collaboration of Judge Guth as Chairman and Judge Dipl.-Chem. Dr. Proksch-Ledig, Judges Dipl.-Chem. Dr. Gerster and Schell and Judge Dipl.-Chem. Dr. Münzberg:

I. European patent 0 907 364 is declared null with effect for the sovereign territory of the Federal Republic of Germany.
II. The Defendant is to bear the costs of the suit
III. The judgement shall be provisionally enforceable on providing a security deposit of 120% regarding the enforced amount.

Facts

The Defendant is the registered owner of European patent 0 907 364 B1 (patent in suit), which was filed as international patent application PCT/GB97/01432 on May 27,

1997, and granted before the European Patent Office in the regional phase, inter alia with effect for the Federal Republic of Germany. The patent in suit claims priority from the British patent application 9611328 of May 31, 1996 and is listed before the German Patent and Trademark Office under DE 697 14 739 T2.

The patent in suit relates to “Sustained Release Pharmaceutical Compositions Comprising a Dibenzothiazepine Derivative” and comprises 20 patent claims, which read as follows:

> 1. A sustained release formulation comprising a gelling agent and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients.
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> 2. A sustained release formulation according to claim 1 such that 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof is released from the formulation, in a controlled fashion over a period of between 8 and 24 hours so that at least 60% of 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof has been released at the end of this period.
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> 3. A sustained release formulation according to claim 1 or claim 2 wherein the gelling agent is hydroxypropyl methylcellulose.
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> 4. A sustained release formulation according to claim 3 comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to

24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof.

5. A sustained release formulation according to claim 3 comprising about 5 to 50% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a) a hydroxypropyl methylcellulose having a viscosity of about 40 to 60 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight, (b) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 28 to 30% by weight and a hydroxypropoxy content of about 7 to 12% by weight, (c) a hydroxypropyl methylcellulose having a viscosity of about 80 to 120 cps, a methoxy content of about 19 to 24% by weight and a hydroxypropoxy content of from about 7 to less than 9% by weight and (d) a hydroxypropyl methylcellulose having a viscosity of about 3,500 to 5,600 cps, a methoxy content of about 19 to 24% by weight and a 45 hydroxypropoxy content of about 7 to 12% by weight, or mixtures thereof with the proviso that if the formulation contains a hydroxypropyl methylcellulose described under (d) above the total amount of hydroxypropyl methylcellulose present in the formulation must be greater than 25.8% by weight.

6. A sustained release formulation according to claim 4 or claim 5 comprising about 5 to 40% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a)- (d) or mixtures thereof.

7. A sustained release formulation according to claim 6 comprising about 8 to 35% by weight of a hydroxypropyl methylcellulose selected from the group consisting of (a)- (d) or mixtures thereof.

8. A formulation according to claim 7 comprising about 10 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a) - (d) or mixtures thereof.

9. A formulation according to claim 8 comprising about 15 to 30% by weight of a hydroxypropyl methylcellulose selected from the groups (a) - (d) or mixtures thereof.

10. A formulation according to anyone of claims 1-9 wherein 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof is present in about 35 to 65% by weight.

11. A formulation according to claim 10 wherein the amount of hydroxypropyl methylcellulose is about 5 to 40%.

12. A formulation according to claims 1-11 wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of microcrystalline cellulose, lactose, magnesium stearate, sodium citrate and povidone.

13. A formulation according to claim 12 wherein the one or more pharmaceutically acceptable excipients are selected from the group consisting of (a) about 4 to 20% by weight of microcrystalline cellulose, (b) about 5 to 20% by weight of lactose, (c) about 1 to 3% by weight of magnesium stearate, (d) about 10 to 30% by weight of sodium citrate and (e) about 1 to 15% by weight of povidone.

14. A formulation according to anyone of claims 1-13 wherein one of the one or more pharmaceutically acceptable excipients is a pH modifier.

15. A formulation according to claim 14 wherein the pH modifier is sodium citrate.

16. A formulation according to any of claims 1-15 wherein 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f][1,4]thiazepine is in the form of a hemifumarate salt.

17. A formulation according to any one of claims 1-16 wherein the formulation is coated.

18. The use of a formulation according to any one of claims 1-17 in the manufacture of a medicament for treating psychotic states or hyperactivity in a warm-blooded animal.

19. A process for preparing a formulation according to any one of claims 1-17 which comprises mixing 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent and other excipients.

20. A process for preparing a formulation according to any one of claims 1-17 which comprises:
(a) mixing 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]-dibenzo[b,f][1,4]thiazepine, or a pharmaceutically acceptable salt thereof, a gelling agent and other excipients;
(b) wet granulating the mixed components;
(c) drying the mixture;
(d) milling the dried mixture;
(e) blending the mixture with a lubricant; and
(f) compressing the blended mixture to form tablets, and optionally coating said tablets.

In their nullity writs, the Claimants attacked the patent in suit in its entirety. They claimed that the subject-matter of claims 1, 3, 10, 18 and 19 was not novel over the relevant prior art. In addition, they claimed that the teaching of the patent was not based on an inventive step. The priority of patent application GB 9611328 was invalidly claimed since it only disclosed a hydrophilic matrix comprising hydroxypropyl methylcellulose whereas claim 1 of the patent in suit names a gelling agent as excipient. These terms could not be used synonymously because the term “hydrophilic matrix” cannot be clearly and unambiguously taken from the term “gelling agent”. Claimant 1 in addition claims that the patent cannot be carried out because

the skilled person would lack crucial information to enable him to carry out the alleged invention.

The Claimants base their arguments in particular on the following documents:

NIK1	EP 0 907 364 B1, patent in suit
NIK1a	GB 9611328
NIK2	DE 697 14 739 T2, German translation of NIK1
NIK3	EP 0 240 228 A1
NIK4	"Arzneiformenlehre" (Ed. P. H. List), 4th edition, 1985 Wissenschaftliche Verlagsgesellschaft mbH Stuttgart, pp. 81, 298 to 300, pp. 312 to 314, pp. 442 to 443, pp. 535 to 544
NIK5	Remington: The Science and Pharmacy, 19th Ed., 1995, Mack Publishing Company Easton, pp. 1660 1667
NIK9	Gefvert, 0. et al., European Neuropsychopharmacology, 1995, p. 347, P-4-65 (= TM8)
NIK11	Alderman, D. A., lnt. J. Pharm. Tech. & Prod. Mfr., 1984,5 (3), pp. 1 to 9
NIK12	US 4 389 393
NIK25	Publication of The Dow Chemical Company: "Formulating for Controlled Release with METHOCEL Premium cellulose ethers", 1995
NIK27	Chang et al., “Sustained Drug Release from Tablets and Particles Through Coating", in: Lieberman, Lachman und Schwartz, Pharmaceutical Dosage Forms, Bd. 3, 1990, Chapter. 4, pp. 199 to 302
NIK29	Farde et al., Arch, Gen. Psych., 1992,49 (7), pp. 538 to 544
NIK30	Wetzel et al., Psychopharmacology 1995, 119, pp. 231 to 238
NIK32	Gelder et al., in:" Oxford Textbook of Psychiatry", 3rd Ed., 1996 Oxford University Press, Oxford, Chapter 9, pp. 246-293 and Chapter 17, pp. 532 to 599
NIK34	Melia, Critical Reviews in Therapeutic Drug Carrier Systems, 1991, 8, pp. 395 to 421

NIK35 "Pharmaceutics: The Science of Dosage Form Design", (Ed.: M. E. Aulton) 1988, CHURCHILL LIVINGSTONE, Langman Group UK Ud, Edinburgh, Chapters 11 and 18, pp. 191 to 211 and 304 to 321

NIK38 Greenberg, R. N., Clinical Therapeutics, 1984,6, pp. 592 to 599

NIK45 American College of Neuropsychopharmacology - 34th Annual Meeting, Dezember 11-15, 1995, San Juan, Puerto Rico, Scientific Abstracts: Poster Session 111, p. 275 - Wong, Y. W. J. et al. as well as Fleischhacker, W. W. et al.,

TM12 EP 0 413 061 A1

TM16 Internet excerpt from the year 2011: Thomson Reuters PharmaTM - Literature & News Report: announcement of Zeneca Ltd. concerning clinical phase III trials with "Seroquel" dated October 2, 1995

TM17 LexisNexis®- Section: Financial News- "Eurand America, INC: Signs Development Agreement with Zeneca Pharmaceuticals, October 3, 1995

The Claimants request

European patent 0 907 364 to be declared null for the sovereign territory of the Federal Republic of Germany.

The Defendant requests

the action to be dismissed,

as an auxiliary motion the action be dismissed provided that the patent in suit is maintained with one of the Auxiliary Requests 1 to 4 as filed with writ of the Defendant dated August 16, 2012.

According to Auxiliary Request 1, the subject sustained-release (SR) formulation is limited to the form of tablets. Auxiliary Request 2 comprises the further limiting feature that the intended amount of gelling agent is to be 5 to 50 wt-%. Auxiliary Request 3 differs from Auxiliary Request 2 in that in case that the gelling agent is

hydroxypropyl methylcellulose, is a hydroxypropyl methylcellulose in accordance with subclaim 4 of the Main Request. In Auxiliary Request 4, the subject-matter of Auxiliary Request 2 is limited to a hydroxypropyl methylcellulose as gelling agent in accordance with subclaim 4 of the Main Request.

The Defendant counters all points of the Claimants and considers the SR formulation claimed in the patent in suit to be novel and inventive over the relevant prior art. The prior art did not give the skilled person a reason to give up on IR formulations and to formulate quetiapine in the manner of the invention. An SR formulation with quetiapine would not have seemed advantageous or favourable to the skilled person at the priority date, either. Rather, given the prior art, the skilled person would have had to assume that quetiapine, in particular in the necessary therapeutic amount, was not suitable for SR formulations but that formulations immediately releasing this active agent were suitable for a successful treatment. According to the Defendant, the overall disclosure of the patent in suit in addition discloses the necessary technical information to the skilled person to be able to use his technical knowledge and experience to carry out the invention according to the patent in suit. Also the priority claim of GB 9611328 is valid because this application already contained all features of the patent in suit.

The Defendant's arguments are in particular based on the following documents:

HE 1 Kapur, S. et al., Arch. Gen. Psychiatry, .2000, 57, pp. 533 to 539

HE 2 American Psychiatric Association: "Practice Guideline for the Treatment of Patients with Schizophrenia", Am. J. Psychiatry, 1977, 154; 4, Supplement, pp. 1 to 63

HE 3 "Sustained and Controlled Release Drug Delivery Systems" (Ed.: J. R. Robinson), 1978, Marcel Dekker, Inc., New York, pp. 78, 79, 92 to 94, 104 to 106, 150 und 167 to 167

HE 4 Decision of the District Court The Hague, Netherlands (Rechtbank's Gravenhage), 397921/HA ZA 11-1977 dated March 7, 2012

HE 4a German translation of the decision HE 4

HE 5 Decision of the US-District Court of New Jersey, Civil Action No. 10-cv-1835 (JAP) (T JB) m. w. C. A. N., dated March 28, 2012

HE 5a German translation of the decision HE 5

HE 6 Opinion by Prof. Dr. Bodmeier dated August 15, 2012

HE 7 Survey "Atypicals Research" from the year 2011 concerning SR formulations

HE 8 Opinion by Prof. Dr. Kasper dated August 15, 2012

HE 9 Kruse et al., International Journal of Clinical Psychopharmacology and Therapeutics, 1994, 32, pp. 452 to 457

HE 10 Völgyi et al., Analytica Chimica Acta, 2010, 673, pp. 40 to 46

HE 11 Translation of decision 202/2012 of the Commercial Court of Barcelona dated July 9, 2012

HE 12 Opinion by Prof. Dr. H.-J. Möller dated September 14, 2012

as well as on the graphs relating to document NIK9 (Annex 1 to the minutes) and the package insert for Seroquel 50 mg (Annex 2 to the minutes) and Seroquel 25 mg (Annex 3 to the minutes) as presented during the oral proceedings.

The nullity actions 3 Ni 43/10 (EP), 3 Ni 24/11 (EP) and 3 Ni 25/11 (EP) were conjoined with decision dated August 29, 2011.

Concerning further details it is referred to the contents of the file.

Reasons for the Decision

I.

The nullity actions based on the reasons insufficiency of disclosure (Art. 138 para 1 lit.b; Art. 83 EPC in connection with Art. II Section 6 para. 1 No. 2 IntPatÜG *[Law on International Patent Conventions]*) and of lack of patentability (Art. 38 para. 1 lit a; Art. 52, 54, 56 EPC in connection with Art. II Section 6 para. 1 No. 1 IntPatÜG) are admissible. They also prove to be justified because the subject-matter of the patent in suit lacks an inventive step both in the form as granted and in the form of the Auxiliary Requests.

II.

1. The patent in suit relates to an SR formulation comprising 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof, the use thereof in the treatment of psychotic conditions or hyperactivity as well as a method for preparing this formulation (cf. patent in suit K1 p. 2 paragraph [0001] in combination with patent claims 1, 18 and 19).

The active agent 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine (=quetiapine), described in European patents EP 240 228 and EP 282 236 as well as US patent 4 879 288, is characterized by its antidopaminergic effect and is used as an antipsychotic drug or in the treatment of hyperactivity. The particular interest in this compound is due to the fact that the risk of side effects such as acute dystonia, acute dyskinesia, pseudo-parkinsonism and dystonia is low compared to other antipsychotic or neuroleptic drugs (cf. patent in suit K1 p. 2 paragraphs [0007] and [0008]).

In the introductory part of the patent in suit it is explained that the provision of pharmaceutical active agents in SR formations for therapeutic and prophylactic treatment would be desirable for various illnesses. This is because such formulations have the advantage that a uniform and constant release rate of the active agents was

ensured over a longer period of time which leads to stable and favourable plasma concentrations without requiring frequent administration of the medicament. In this context, numerous SR formulations were known in which gelling agents such as hydroxypropyl methylcellulose were used. Preparing such formulations with soluble agents, however, always involves problems. For example it proved inter alia problematic to achieve the required solution profiles and/or to control the release rate of the soluble active agent because SR formulations of soluble agents tend to a phenomenon known as “dose dumping”. This means that the release of the active agent is at first delayed a bit but the release rate is then very high when the release starts. In addition, such plasma concentrations of the active agent tend to fluctuate in such formulations which can lead to toxic reactions. Further, day-to-day fluctuations (diurnal variations) of the active agent were observed in the plasma concentrations, too (cf. patent in suit K1 p.2 para. [0002] and [0003]).

2. The objective technical problem underlying the patent in suit according to current case law is to be determined solely based on what was actually invented, i.e. the problem has to be directed to the result of the invention. This is why what was actually achieved compared to the prior art is to form the basis for finding the technical problem, wherein the prior art and advantages of the invention and disadvantaged of previously known solutions form the basis for its formulation. The process of determining the underlying objective problem may be aided by information on the problem of the invention contained in the description that contain an indication of how to correctly understand the patent claim (BGH GRUR 2012, 803,805 Tz. [31] m. w. N. - Calcipotriol Monohydrat and Schulte PatG 8th edition Section 1 marginal numbers 62, 63 and 65, Busse PatG 7th edition Section 1 marginal numbers 70, 74 to 76, Benkard PatG 10th edition Section 1 marginal numbers 55a, 56; Section 34 marginal numbers 18 to 20).

What was presently invented is an SR formulation containing quetiapine, a gelling agent and one or more excipients. In the patent document, which has to be consulted for determining the problem to be solved (cf. BGH GRUR 2012, 803,805 Tz. [32] - Calcipotriol-Monohydrat), it is on the one hand explained in relation to the problem to be solved that it is desirable to provide pharmaceutical active agents in SR form in order to ensure a uniform and constant release rate over a longer period of time and

thus a stable plasma concentration – without the necessity of a frequent administration of the active agent. On the other hand, the disposition in particular of readily soluble active agents to “dose dumping” is described as a technical problem of such formulations, leading to fluctuations of the plasma concentration of the active agent and thus possibly to toxic reaction. Thus, what the present formulation achieves over the composition known at the priority date which releases the active agent quetiapine immediately is that the active agent is released constantly over a longer period of time while at the same time the plasma profiles are smoothed out by which more uniform and stable plasma concentrations of the active agent can be achieved. It is also part of the achievement that due to that constant release, the formulation containing the active agent has to be administered less frequently (cf. patent in suit K1 p. 2 para. [0002] to [0006], p. 5 para. [00037] to p. 6 para. [0038] in connection with Fig. 1 and Fig. 2).

In light of the above, the patent in suit concerns the technical problem of providing a formulation of quetiapine which releases the active agent over a longer period of time in a generally uniform and constant manner and requires less frequent administration.

The Senate cannot follow the Defendant’s argumentation that the problem is to be solely seen in the provision of a different or better formulation. Such a general formulation of a technical problem without further concretizing the goal is not in accordance with the general practice. The skilled person will usually rather be asked to look for solutions to defined problems that can belong to his area of expertise. The publication according to the press release TM17 also contradicts this definition of the problem comprising any possible formulation. This is because based on this definition it becomes clear that the experts at the relevant date had already considered SR formulations as an alternative to the known dosage form releasing quetiapine immediately. The patent in suit on the other hand does not contain any hints that any kind of formulation known to the skilled person would have been a possible alternative to the known dosage form that releases quetiapine immediately to achieve an unspecified improvement. The patent in suit rather focusses on the provision of SR formulations and the problems occurring when soluble agents are used in such dosage forms (cf. patent in suit K1 p. 2 para. [0002] and [0003]).

The Defendant further claimed that general case law dictates that anything that the patent actually achieves needs to be considered when determining the problem. According to the Defendant – referring in particular to the survey HE 7 from the year 2011 – the provision of the SR formulation according to the patent lead to an improvement in the treatment, like a quicker adjustment of the therapeutic dose, a less sedative effect compared to IR formulations and a surprising range of indications. These insights, which only came to light after the priority date, however, cannot result in a different definition of the underlying problem. This is because the knowledge gained after the priority or filing date have no influence on the determined objective technical problem (cf. BGH GRUR 1991, 811 Ls. 1., 813 111.2. - "Falzmaschine" and Schulte, PatG, 8th edition., Section 4 marginal number 37 item g and Mes, PatG, 3rd edition, Section 4 marginal number 11).

3. The problem is solved according to claim 1 by a

1. sustained release formulation comprising
2. a gelling agent and
3. 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof,
4. together with one or more pharmaceutically acceptable excipients.

According to claim 18, the problem is further solved by the use of this formulation for the treatment of psychotic states or hyperactivity in a warm-blooded animal.

Further, according to claim 19 the problem is solved by a method for the preparation of a formulation as claimed in claim 1.

4. The relevant skilled person in the present case is a team comprising at least one pharmacist holding a doctorate in pharmaceutical technology and having several years of experience in developing and producing formulations of medicaments with controlled release and a physician who is experienced in the treatment of psychotic illnesses.

III.

Patent claims 1 to 20 according to the main request prove to be invalid due to a lack of patentability.

1. The question of whether or not the priority claim of the patent application GB 9611328 is valid is irrelevant in the end because none of the documents relevant for the decision has a publication date between the priority date and the filing date. It is also irrelevant for the decision in how far the concerns offered by the Claimants concerning the sufficiency of disclosure are justified or whether the claimed SR formulation lacks novelty. The SR formulation according to claim 1 is null because its provision is at least not based on an inventive step (in the sense of Art. 56 EPC).

2. The skilled person could start from the abstract NIK9 by the authors Gefvert, O. et al for the solution of the problem underlying the patent in suit. This contribution concerns the administration frequency of the medicament Seroquel^{TM}, which is an IR formulation of the active agent quetiapine taking into account the dopamine and serotonin receptor occupancy. The study described therein is based on the idea that considering the essential requirement of patient compliance for schizophrenic patients a more favourable dosing regime than the customary one at that time, i.e. TID and QID (three and four times a day) would be advantageous. During this study it was then assessed in how far a twice daily administration might be enough to achieve the 5HT2/D2 (=serotonin/dopamine) receptor occupancy which was considered necessary for successful treatment. To this end, the medicament Seroquel^{TM} was administered TID to a group of patients over a period of four weeks. After the last dose was administered, the D2 and 5HT2 receptor occupancy as well as the plasma concentration of the active agent was measured in per cent in predetermined intervals. While the value for the 5HT2 receptor occupancy was still at 50% after 26 hours – as can be seen from the table -, this value was at 0% for the D2 receptor compared to a value of 44% after 2 hours. Further, a drop in the plasma level of the active agent from 402,8 ng/l after 2 hours to a value of 7,2 ng/ml after 26 hours was observed. Document NIK9 does thus not only indicate to the skilled person that under the conditions described therein the values of two of the three

factors the authors obviously considered essential to maintain the efficacy significantly dropped within 26 hours. The skilled person will conclude that these values – as incidentally also confirmed by the diagrams submitted by the Defendant during the oral proceedings, which are based on theoretical assumptions – will also tend towards 0 two hours earlier, i.e. 24 hours after taking the medicament. The experts at the relevant date, however considered the occupancy of both receptors to be essential for a successful treatment of psychotic illnesses – as suggested by all parties. To avoid toxic plasma peaks of the active agent and to maintain a therapeutically effective level, a uniform plasma level of the active agents was also aimed at (cf. e.g. NIK4 p. 535 para. 2 and 3). The document thus teaches the skilled person that in light of the values given in the table the frequency of administration may be lowered but that a once daily administration of a medicament immediately releasing quetiapine will not be sufficient to ensure an effective treatment. Incidentally, this also correlates with the aim of the described study given at the beginning of the publication according to which the realisation of a twice daily administration was the focus of the study. The fact that the results described in document NIK9 were actually considered feasible in contrast to a once daily administration of Seroquel^{TM} described in document NIK9 can be taken from the hint given at the end of the abstract NIK9 to the SAFARI study which was an efficacy study running at the same time. This study also only explored the possibility of reducing the administration frequency of an IR formulation from three times a day to twice a day - but to not once a day - while at the same time maintaining efficacy (cf. TM16 page 1 para. 5). Thus, the conclusion of the authors of the abstract NIK9, according to which a once to twice daily administration of the active agent in the dose described therein may be sufficient to maintain the necessary 5HT2/D2 receptor occupancy, may be that a once daily administration might be commendable considering patient compliance in patients suffering from schizophrenia but that on the down side the D2 receptor was no longer occupied. But the further actions of the authors themselves proves that they did not consider the known IR oral dosage form of quetiapine for this objective in practice.

However, the skilled person was motivated to consider a formulation for the realisation of an administration frequency reduced to once a day which is based on a different release profile than the known IR oral dosage form of quetiapine by the

press release TM17. With this press release, the skilled person was informed before the priority date that there were plans to develop a once daily dosage form for quetiapine. The reason for this is the corresponding expectation of clinical advantages of a larger scale concerning efficacy and side effects, in particular when treating patients suffering from schizophrenia. The skilled person understands – reference is made to the textbook "Pharmaceutics: The Science of Dosage Form Design" M. E. Aulton (Ed.) (= NIK35) - a “once daily dosage form” to be a formulation that releases the active agent over a longer period of time, i.e. dosage forms that are known as SR formulation in the art (cf. NIK35 pp. 315/316, paragraph bridging left and right columns). A company that specialises – as can also be taken from this document - in the preparation of oral compositions releasing active agent, whose main field is in particular the preparation of controlled-release systems, i.e. also SR formulations, was charged with this development that was announced in TM17 (cf. also NIK5 p. 1661 left col. para. 2 and 4 and NIK35 p. 206 left col. para. 1 and 2).

It was thus obvious to seize the motivation provided by the press release TM17 and to implement the same, i.e. to consider an SR formulation for the desired once daily administration of quetiapine. This is all the more true because the skilled person – based on his general technical knowledge - could assume that with such formulations the frequency of administration could definitely be further reduced and that such formulations will not only improve patient compliance but their administration will also lead to a constant plasma level of the active agent, which is a particularly important clinical advantage (cf. e.g. NIK5 p. 1662 left/right col. "Potential Advantages of Sustained Drug Therapy" as well as NIK35 p. 209 left/right col. "Potential advantages of sustained release drug therapy over conventional drug therapy" and paragraph bridging pp. 315/316).

The feature of claim 1 of formulating the active agent quetiapine using a gelling agent can also not establish an inventive step. This is because the skilled person was aware from the US patent NIK12 that matrix systems based on gelling agents like hydroxyproyl methylcellulose were suitable for formulating a variety of active agents with vastly different structures and thus dissolution rates when providing SR oral dosage forms at the relevant date (cf. claim 1 in combination with col. 4 ll. 22 to 65). In particular it is also pointed out in this document that the controlled release of an

active agent within a drug treatment of psychotropic disorders like manic depression or schizophrenia is very important (cf. col. 6, ll. 5 to 23). According to this document, the preparation of such formulations is furthermore not only simple and economic. The tablets prepared with the use of gelling agents in addition show no side effects of the gelling agent, a very good release rate of the active agent, which emphasises its efficacy, and a well adjustable release rate (cf. col. 5, ll. 5 to 50). In light of the teaching of document NIK12 it was thus obvious, when solving the problem of the patent in suit, to consider the hydroxypropyl methylcelluloses as matrix former as described in the patent in suit for the SR formulation containing quetiapine as suggested in the press release TM17. When following this route, the skilled person could assume from the beginning that the advantages he aimed for, like a more uniform and stable plasma concentration of the active agent and a lower administration frequency than usual with IR formulations, would be achieved. This is because these are not only properties that are described in US patent NIK12 for dosage forms made from those matrix builders (cf. col. 1 ll. 9 to 20, col. 2 ll. 33 to38, col. 3 ll. 25 to 39, col. 4 ll. 29 to 35, col. 5 ll. 9 to 23 and 32 to 50 and col. 6 ll. 10 to 13), but also properties that are inherent to SR formulation (cf. NIK35 paragraph bridging pp. 315/316). In order to test in how far following the steps given in claim 1 actually leads to the desired properties or advantages, the skilled person could carry out some routine tests that do not require any inventive activity.

The advantages offered as proof by the Defendant of a more rapid adjustment to the therapeutic dose, a less sedative effect compared to the IR formulation and a surprising range of indications are to be considered to be the result of actions made obvious by the prior art which are not suitable to justify patentability (cf. BGH GRUR 2003, 693 - Hochdruckreiniger).

The Defendant further submitted that the skilled person would have had no motivation to consider SR formulations for the active agent quetiapine for a once daily dosage form because already the parent application NIK3 p. 4 ll. 32 to 50 teaches that this active agent could also be administered only once a day in conventionally formulated dosage forms and still achieve the desired effect. These arguments, however, cannot change the outcome. The application does not contain any information on how the desired treatment success can actually be achieved with

such a dosing scheme that goes beyond the general dosing information. The skilled person only gets information on this from the abstract NIK9 which, however, teaches him that in order to achieve the desired success an IR dosage form, i.e. a conventionally formulated dosage form – as described in the publication NIK3 – should be administered at least twice a day.

Also the argument of the Defendant that document NIK9 motivated the skilled person to use a higher dose of the active agent for realising a once daily dosage form, which is why he would not have considered SR formulations because these are not suitable for larger amounts of active agent cannot convince the Senate. Both according to the abstract NIK9 and the abstract published with document NIK45 by the author W.W: Fleischhacker et al. the dose of 450 mg corresponding to the usual triple dose of the medicament SEROQUEL^{TM} is considered to be sufficiently effective in a twice daily dose. This concentration of active agent is therefore – it is also referred in this context to Examples 1 and 12 of the patent in suit – the starting point for the planned development of a once daily dosage form, independent of whether it is an IR or an SR formulation. For this reason, the skilled person must in both cases include this amount of active agent in his considerations and thus also that dosage forms prepared on the basis of this concentration of active agent will necessarily have a larger volume. In this context the skilled person will not be prevented by an amount of active agent of about 450 mg from considering an SR formulation for realising his goal because he already knows from the prior art of corresponding feasible formulations with much higher amounts of active agents (cf. NIK12 col. 3 ll. 25 to 39 and col. 6 Examples 1-2). The skilled person will thus not a priori exclude such formulation questions in his quest of solving the problem underlying the patent in suit but will rather consider them promising for his needs. In how far these fulfil the technical requirements in the case of quetiapine can then be shown by tests with which the skilled person familiar with the formulation of such dosage forms can gain an overview over the actual feasibility.

Also the reference the Defendant made in this context to documents NIK29, NIK30 and NIK32 cannot lead to a different assessment of the facts. This is because these documents do also not contain a hint that the skilled person would have been

prompted to consider a higher dose than that mentioned in document NIK9 for the preparation of a once daily dosage form.

The scientific article NIK29 by the authors L. Farde et al. deals with the relations between D2 dopamine receptor occupancy and the occurrence of extrapyramidal syndrome (EPS). According to the article, patients with EPS had a significantly higher D2 dopamine receptor occupancy than patients without EPS (cf. p. 542 right col. para. 3 to p. 543 left col. para. 2 and 4). A significantly lower D2 dopamine receptor occupancy than that observed with classic antipsychotic drugs was observed in the case of the atypical antipsychotic drug clozapine, even if its dose was on the upper level of clinical trials. An occupancy that can be compared to typical antipsychotic drugs pared with the occurrence of extrapyramidal syndrome was only observed with very high doses in this case (cf. p. 543 left col. para. 3, 5 and 6). In how far there was a correlation between the dopamine receptor occupancy and antipsychotic effect of the tested antipsychotic drugs was not discussed in the article (cf. p. 543 right col. para. 3). The information on p. 543 left col. para.6, according to which a receptor occupancy comparable to classic antipsychotic drugs could be observed only with a daily dose of clozapine of more than 2000 mg, does thus not generally imply that the dosage amount of the antipsychotic drug always has to be realigned with the D2 dopamine receptor occupancy found with classic antipsychotic drugs. The same conclusion can be drawn from the publication NIK30 by the authors H. Wetzel et al., which relates to studies on the active agent quetiapine. The publication ends in the summary that the administration of up to 750 mg quetiapine per day did not lead to a completely satisfactory antipsychotic effect in the described studies (cf. p. 237 right col. para. 3). The document does not, however, contain any hint as to which dosing regime was used in the described studies. The results of these studies do therefore not allow for any conclusions to be drawn as to the concentrations of active agent for an SR formulation. This is all the more true because documents NIK9 and NIK45 teach the skilled person that with a dose partitioned off over a day – irrespective of whether it is a twice or three times daily administration – dosage amounts of 450 mg of quetiapine are sufficient for reaching the desired effect. The information on the dosing of antipsychotic drugs in the textbook “Oxford Textbook of Psychiatry” by the authors M. Gelder et al. (= NIK32) are also not suitable to prove the Defendant’s arguments. On the contrary, in this context it is warned against the use of too high

doses because these might cause severe side effects (cf. paragraph bridging pp. 555/556).

The Senate can also not follow the further argument of the Defendant, that the plasma half life of quetiapine allowed no conclusions concerning the necessary dose and that that is why the skilled person would not have had cause to consider SR formulation of quetiapine for solving the problem underlying the patent in suit, even if he was aware of the course of plasma half life over a period of 26 hours as described in the abstract NIK9. Not only the general doctrine contradicts this understanding (cf. NIK4 p. 535 para. 2 and 3) but also the study NIK45 carried out at the same time which focusses only on a twice a day administration of quetiapine in a concentration of 225 mg each leading to the desired effect. This, however, is a dosing scheme by which – as can be seen from the table in abstract NIK9 – a more uniform plasma level of the active agent can be maintained than with a single dose of 450 mg of a IR dosage form.

The Defendant further submitted referring to the textbook ”Pharmaceutical Dosage Forms: Tablets" edited by H. A. Lieberman et al. (= NIK27) and the article by the authors G. Völgyi et al. (= HE10) published in 2010 that the skilled person was further kept from considering quetiapine for an SR formulation because this active agent showed too large variances in the different physiological pH values. The patent in suit K1, however, does not contain any hints that specific measures that go beyond the average know how of the skilled person had to be taken to formulate quetiapine that way. P. 3 para. [0017] rather lists among optionally added excipients inter alia pH regulating agents. These, however, are additives whose use for the regulation of the solubility of the active agent are known to the skilled person in connection with gelling agents and the preparation of SR formulations – as can be seen from overview article NIK34 paragraph bridging pp. 406/407.

The Defendant finally claimed that with drugs containing quetiapine there were no problems with patient compliance with patients suffering from schizophrenia because according to current expert opinion there was no difference between a once daily and a twice daily administration. For proof of this, the Defendant referred to documents HE9 and NIK38. This argumentation can also not convince the Senate. At the

relevant date there might have been differing opinions in the expert world concerning the maintenance of the compliance necessary for successful treatment. Irrespective of the necessity of compliance described in the cited documents, in particular with patients suffering from schizophrenia, this problem is pointed out expressis verbis in documents NIK9, NIK16 and TM17 in connection with the active agent quetiapine. And in the press release TM17 it is furthermore explicitly mentioned that the reduction to a once daily administration was the goal for the development of a dosing unit fulfilling this requirement.

The subject-matter of patent claim 1 is therefore invalid because it lacks inventive step.

3. The remaining patent claims of the Main Request do not require further, isolated examination because the Defendant explained during the oral proceedings that the sets of claims of the Main Request and the Auxiliary Requests are to be understood as complete sets and that the patent in suit was defended in the order of the Auxiliary Requests (cf. BGH GRUR 2007, 862, 864 – Informationsübermittlungsverfahren II; BPatG GRUR 2009, 46 - Ionenaustauschverfahren).

III.

The versions of the claim sets defended by the Defendant in Auxiliary Requests 1-4 equally prove to be invalid due to a lack of inventive step. The Defendant also failed to submit that they contained separate patentable subject-matter.

1. The subject-matter of patent claim 1 of the 1st Auxiliary Request differs from the subject-matter of patent claim 1 of the Main Request in that it is directed to an SR formulation in the form of a tablet. This is a dosage form that was not only already described as suitable in the parent application NIK3 for the administration of the active agent quetiapine (cf. p. 4 ll. 35 to 37) but was also commonly used for SR formulations that contain gelling agents as matrix builders (cf. NIK12 col. 5 ll. 24 to 50). For this reason, the claim provides no further facts than those given for patent claim 1 according to the Main Request. The reasons given in that context therefore also apply here.

2. The same is true for patent claim 1 according to the 2nd Auxiliary Request. This one differs from patent claim 1 of the Main Request in the specification of the amount of gelling agent of 5 to 50 wt%. This, however, is a usual amount in the preparation of SR formulations containing gelling agent as matrix builders, as can be seen from US patent NIK12 (cf. Examples 1 to 12).

3. The requirement according to claim 1 of both the 3rd and the 4th Auxiliary Request according to which – in the case of the 3rd Auxiliary Request optionally – the gelling agent is selected from the listed, differently substitutes hydroxypropyl methylcelluloses (a) to (d) cannot lead to a different assessment of the facts. This is because these hydroxypropyl methylcelluloses are not only frequently used matrix builders in the preparation of SR formulations as can be seen e.g. from document NIK25 that can also be combined with each other depending on the requirements (cf. p. 1, p. 2 left col para. 1 to 4 in combination with p. 5, p. 14 left col para. 8 and right col.). The skilled person therefore also had motivation to consider these substituted hydroxypropyl methylcelluloses for his needs because document NIK12 teaches that these substituted hydroxypropyl methylcelluloses are suitable for the preparation of SR formulations of structurally different active agents whose amounts vary a lot – in particular also in mixtures of these polymers (patent claims 1 and 10 in combination with description col. 1 ll. 9 to 21, col. 2 ll. 40 to 47, col. 3 ll. 15 to 38 and col. 4 ll. 4 to 28 and 47 to 65 as well as Examples 1 to 27). The limitation of the gelling agent to the matrix builders listed in both claims 1 does therefore not add anything to support inventive step. Thus, the considerations concerning the Main Request apply here as well and are referred to herewith.

IV.

The order for payment of costs is based on Section 84 para. 2 PatG in combination with Section 91 para. 1 ZPO *[Civil procedure code of Germany]*. The decision concerning the provisional enforceability results from Section 99 para. 1 PatG in connection with Section 709 ZPO.

Guth Dr. Proksch-Ledig Gerster Schell Dr. Münzberg