Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2020-01-21
Docket Number / Aktenzeichen:	X ZR 65/18
Name of Decision / Name der Entscheidung:	Tadalafil

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 65/18

Pronounced on:
21 January 2020
Zöller
Judicial Secretary
as Clerk of the
Court Registry

in the patent nullity proceedings

Tadalafil

EPC Art. 56

If the skilled person had reason on the priority date to conduct complete studies on the dose-effect relationship of a particular active ingredient at some, possibly later, point in time, a dosage that proves to be beneficial on the basis of such a study is suggested by the state of the art.

Federal Court of Justice, judgment of 21 January 2020 – X ZR 65/18 – Federal Patent Court

ECLI:DE:BGH:2020:210120UXZR65.18.0

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 21 January 2020, attended by the judges Dr. Bacher, Dr. Grabinski and Dr. Deichfuß, the judge Dr. Rombach and the judge Dr. Rensen

ruled that:

The appeal against the judgment of the 3rd Senate (Nullity Senate) of the Federal Patent Court of October 24, 2017, is dismissed at the expense of the defendant.

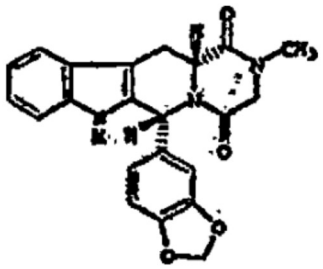
By operation of law

Facts of the case:

1 The defendant is the proprietor of European patent 1 173 181 (patent in suit), which was filed on April 26, 2000, claiming priority of a U.S. application dated April 30, 1999, and which was granted with effect for the Federal Republic of Germany. The patent in suit relates to an inhibitor of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 (PDE5 inhibitor) and its use in a pharmaceutical unit dosage form.

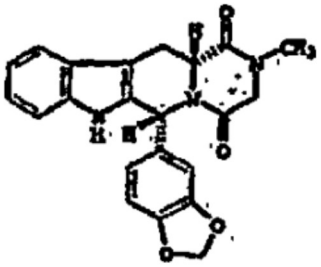
2 Patent claim 1, to which claims 2 to 9 are referred back, and patent claim 10, to which claims 11 to 17 are referred back, have been given the following version in the language of the proceedings after conducting limitation proceedings before the European Patent Office [amendments to the granted version are highlighted]:

"1. A pharmaceutical unit dosage composition comprising 1 to 20 5 mg of a compound having the structural formula:



said unit dosage form suitable for oral administration up to a maximum total dose of 20 5 mg per day.

~~13~~10. Use of a unit dose containing 1 to 20 5 mg of a compound having the structure



for the manufacture of a medicament for administration up to a maxi-mum total dose of 20 5 mg of said compound per day in a method of treating sexual dysfunction in a patient in need thereof."

3 The plaintiffs have argued that the subject matter of the patent in suit is not patentable. In addition, they consider the use claims relating to the treatment of a disorder of sexual arousal in women to be non-executable. The first applicant further argued that the subject matter of the patent in suit goes beyond the content of the original application and that its scope of protection has been extended. The defendant defended the patent in suit as granted and with four auxiliary requests. The Patent Court declared the patent in suit invalid.

4 In its appeal, the defendant defends the patent in suit lastly primarily in the version of the first-instance auxiliary request 2 (second-instance main request) and alternatively with the first-instance main request (second-instance auxiliary request I), with patent claims 3 and 7 and the subclaims relating thereto in the version of the second-instance main request (second-instance auxiliary requests I a and I b) as well as the first-instance auxiliary requests 3 and 4 (second-instance auxiliary requests II and III). The plaintiffs oppose the appeal.

Grounds of the decision:

5 The admissible appeal is unsuccessful on the merits.

6 I. The patent in suit concerns an inhibitor of cyclic guanosine 3',5'-monophosphate-specific phosphodiesterase type 5 (PDE5) and its use in a pharmaceutical unit dosage form.

7 1. According to the statements in the patent in suit, PDE inhibitors can be used for the treatment of disease states in which the modulation of smooth muscle, renal, hemostasis, inflammatory or endocrine function is desired due to their biochemical, physiological and clinical effects. Because of its presence in vascular smooth muscle and the penile corpus cavernosum, PDE5 is an attractive target in the treatment of sexual dysfunction (para. 3).

8 A well-known PDE5 inhibitor is the active ingredient sildenafil, which is marketed in tablet form with dosage units of 25, 50 and 100 mg under the trade name Viagra. Its IC50 (concentration at which an inhibition of 50% of the enzyme quantity present is observed in vitro, cf. para. 18) is stated in previous publications to be 3 or 3.9 nM (para. 4).

9 However, sildenafil has a relative lack of selectivity for PDE5, to which impairments in color vision are attributable. In addition, facial flushing may occur. In patients with such impairments, the use of sildenafil would be limited. In patients taking organic nitrates, it is even strictly contraindicated. Therefore, notwithstanding the availability of sildenafil, there was a need to find improved pharmaceutical products useful for the treatment of sexual dysfunction (paras. 5 and 6).

10 US patent specification 5 859 006 (Daugan) discloses certain tetracyclic derivatives that are potent inhibitors of PDE or PDE5. The IC50 of these compounds was in the range of 1nM to 10 µM. The unit dose forms contained 0.2 to 400 mg of active compound. Significant side effects were not disclosed. International application WO 97/03675 (Daugan [NIK5/NiK4]) disclosed the use of tetracyclic derivatives in the treatment of impotence (para. 7).

11 2. Against this background, the patent in suit concerns the technical problem of providing another PDE5 inhibitor for the effective treatment of sexual dysfunction that has as few side effects as possible.

12 According to the case law of the Senate, advantages that have only become attainable as a result of the invention must be disregarded when determining the problem underlying the invention, as must elements that are part of the technical solution (Federal Court of Justice, judgment of 11 November 2014 - X ZR 128/09, GRUR 2015, 356 marginal no. 9 - Repaglinid). Rather, the technical problem underlying the invention must be formulated in such a general and neutral manner that the question of which suggestions the skilled person received from the prior art arises solely when examining the inventive step (Federal Court of Justice, judgment of 13 January 2015 - X ZR 41/13, GRUR 2015, 352 marginal no. 17 - Quetiapin).

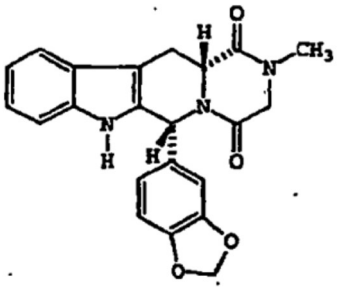
13 From there the problem underlying the invention of the patent in suit lies contrary to the view of the defendant not in providing an active substance for the treatment of sexual dysfunction, which is orally effective like Sildenafil, but does not have its disturbing side effects, since thereby advantages of the patent solution are considered.

14 However, the Patent Court, which saw the problem underlying the invention in the provision of dosages of tadalafil for effective therapy for sexual dysfunction, cannot be agreed with either, since the choice of tadalafil is also already an element of the technical solution and must therefore be left out of consideration in the task.

15 3. The technical problem is to be achieved according to patent claim 1 in the version of the most recently filed main request by a pharmaceutical unit-dose-composition, the features of which can be structured as follows (changes compared to the version after the limitation proceedings before the European Patent Office are highlighted):

1. Pharmazeutische Einheitsdosiszusammensetzung
(Pharmaceutical unit dosage composition),

2. die eine Verbindung umfasst mit der Strukturformel
(comprising a compound having the structural formula),



3. die 1 bis 5 mg dieser Verbindung umfasst
(comprising 1 to 5 mg of this compound),

4. ~~wobei die Einheitsdosisform geeignet ist~~ zur täglichen oralen Verabreichung
(~~said unit dosage form suitable~~ for daily oral administration)

5. von bis zu einer maximalen Gesamtdosis von 5 mg pro Tag
(up to a maximum total dose of 5 mg per day).

16 4. As the Patent Court correctly decided without objection by the parties, the skilled person is a team comprising a pharmacologist, a medical doctor with several years of professional experience in the field of therapy of sexual dysfunctions and a pharmaceutical technologist.

17 5. From the point of view of such a skilled person, patent claim 1 as amended by the most recently filed main request protects a pharmaceutical unit dose composition comprising 1 to 5 mg of tadalafil for daily oral administration of up to a maximum total dose of 5 mg per day.

18 In this regard, the Patent Court is to be distinguished between daily oral administration and administration on demand ("on demand").

19 While on demand dosing is defined in the description as intermittent administration of compound (I) prior to expected sexual activity (para. 74), daily oral administration is to be understood as oral administration at daily intervals independent of expected sexual activity.

20 II. The Patent Court essentially reasoned its decision as follows:

21 Whether the subject-matter of patent claim 1 as amended by the main request at first instance was inadmissibly broadened, whether the limitation in

the proceedings before the European Patent Office led to an inadmissible broadening of the scope of protection, and whether the invention was disclosed in such a way that the skilled person could carry it out, did not require a decision. In any case, the protected subject matter was not based on an inventive step.

22 NIK5/NiK4 and application WO 95/19978 (NIK4) concern a pharmaceutical composition comprising tadalafil for the treatment of sexual dysfunction, administered orally in the form of tablets or capsules with an active ingredient content of 0.2 to 400 mg for a maximum daily dose of 0.5 to 800 mg. These broad dose ranges indicated that they were the result of safety and tolerability testing typically conducted as part of pharmacodynamics studies during Phase I clinical trials. The therapeutically effective daily maximum oral dose of tadalafil as well as information on the dosage in the composition could therefore not be inferred from these citations. In view of this, the skilled person would conduct targeted dose-finding studies. He would try to achieve the desired effect and avoid side effects as far as possible. In this context, it is customary to start with very low initial doses and to increase the dose if tolerated.

23 With regard to tadalafil, the expert will also be guided by sildenafil, starting from NIK5/NiK4. From the publication of Goldstein et al (British Journal of Urology, 1997, 80, Suppl. 2, Abstract 356, Table [NiK6]) clinical tests with sildenafil had been known, which had already shown a good effect with a daily oral dosage of 5 mg. According to this study, finding a maximum daily total dose of 5 mg tadalafil was a usual measure that could be attributed to the area of responsibility of the measure.

24 The skilled person also had a reasonable expectation of success with regard to the dosage according to the patent in suit. The fact that a good effect had already been described for sildenafil at a dosage of 5 mg had motivated the skilled person to consider dosages in this range. He was encouraged in this by the IC50 value, which is an important indication of the efficacy of an active substance and is at least 33% higher for sildenafil than for tadalafil.

25 It is true that the IC50 value for tadalafil was only measured in vitro. Nevertheless, it is a value recognized by experts for the assessment of

therapeutic efficacy. In addition, it was known that PDE5 inhibition was the biochemical basis for the therapeutic treatment of sexual dysfunction.

26 In contrast, NIK5/NiK4 only disclosed examples with 50 mg tadalafil. However, from a technical point of view, this was not an argument against considering lower concentrations. The examples were merely examples of formulation in principle and not the result of dose-finding trials, which were only the subject of the clinical trial in phase II. Moreover, the examples do not claim to indicate a particularly suitable dosage for the active substance.

27 The subject-matter of patent claim 1 in the version of the first-instance auxiliary request 2 goes beyond the content of the documents originally filed. There, the daily administration of tadalafil was mentioned only in examples 5 and 6. These concerned only a dose of 10 mg and 5 to 20 mg. In contrast, the daily administration of a dose of 1 to 5 mg is not disclosed. Insofar as a dose of 2 mg of tadalafil is described in example 7, this is only administered on demand, i.e. in anticipation of sexual activity.

28 III. This assessment withstands the attacks of the appeal, at least in the result.

29 1. Contrary to the opinion expressed by the plaintiff, the order of the applications with which the defendant defends the patent in suit, as stated last, does not lack the necessary interest in legal protection. The change of the order of the requests is also not inadmissible due to lateness.

30 a) In patent nullity proceedings, the defendant is in principle free to defend the patent as amended.

31 From the point of view of the interest in legal protection, it is basically up to the defendant to decide which amendments it wants to make and in which order it wants to file several auxiliary requests. In general, it will be interested in the broadest possible subject matter. Depending on the constellation of the individual case, however, a narrower version may be more attractive from its point of view, but its admissibility is not certain. Against this background, it is not objectionable if the defendant primarily promotes a narrower and only in the alternative a broader version.

32 b) Sec. 117 Patent Act and Sec. 531(2) Code of Civil Procedure do not preclude the rearrangement of the order of the requests, if only because the defendant has already filed all requests filed in the second instance in the first instance and the Patent Court has dismissed the action.

33 The Patent Court has decided on all applications filed in the first instance. In view of this, these requests do not constitute new means of defense in the second instance even if they are filed in an amended order. 2.

34 2. Whether the subject-matter defended by the main request of the second instance goes beyond the content of the documents originally filed, as decided by the Patent Court with regard to the subject-matter of the auxiliary request 2 of the first instance, does not need to be decided, nor does the question whether this constitutes an inadmissible extension of the scope of protection.

35 3. The subject matter defended by the second-instance main request is in any case not based on an inventive step and is thus not patentable.

36 a) For the skilled person, who was concerned with the task of providing a further PDE5 inhibitor for the effective treatment of sexual dysfunction with as few side effects as possible, NIK5/NiK4 was of great interest as a starting point for his considerations, since it deals with the use of tetracyclic derivatives as selective inhibitors of PDE or PDE5 for the treatment of erectile dysfunction.

37 aa) In this respect, the citation proposes a large number of compounds, although two specific compounds (compounds A and B) are highlighted as particularly suitable (NIK5/NiK4 p. 5 line 23 ff.). Only these two compounds are also the subject of the embodiment examples and claim 2 of the citation. One of them (compound A) is tadalafil (6R,12aR)-2,3,6,7,12,12a-hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino[2',1':6,1]pyrido[3,4-b]indole-1,4-dione).

38 Against this background, the skilled person had reason to consider tadalafil as a possible alternative to sildenafil for the treatment of sexual dysfunction.

39 bb) The fact that NIK5/NiK4 does not indicate a preference for one of the two compounds highlighted as particularly suitable does not lead to a different assessment. In view of the limited number of possibilities thus indicated, the skilled person had a reason to subject both to closer consideration.

40 This applies even if there should have been indications to consider the compound B disclosed in NIK5/NiK4 as the first one. If several alternatives come into consideration for the skilled person, several of them may be obvious. In this context, it is irrelevant which of these alternative solutions the skilled person would have considered first (Federal Court of Justice, judgment of 16 February 2016 - X ZR 5/14, GRUR 2016, 1023 marginal no. 36 - Anrufroutingverfahren; judgment of 16 September 2019 - X ZR 106/17, BeckRS 2019, 27168 marginal no. 44 - Kathetervorrichtung).

41 b) Contrary to the opinion of the appeal, there was sufficient prospect of success for the skilled person to conduct clinical studies with tadalafil on the basis of the NIK5/NiK4.

42 aa) It can be left open whether the broad dosage range of 0.5 to 800 mg specified in NIK5/NiK4 for the oral administration of tadalafil (NIK5/NiK4 p. 5 para. 1) permits the conclusion drawn by the Patent Court that this information is based on safety and tolerability tests, such as typically take place during Phase I clinical trials. Even if this were to be denied, the skilled person was in any case encouraged by NIK5/NiK4 to initially consider tadalafil for clinical trials of this phase, in which the safety and tolerability of the drug are regularly examined in particular. The positive results of such a study subsequently gave him cause for clinical studies of phases II and III, in which efficacy and the dose-response relationship are also regularly tested (cf. Jaehde, et al., Lehr-buch der Klinischen Pharmazie, 1988 p. 104 ff. [NiK21 and NiK21a]; Karzel/Liedtke, Einführung in die Arzneimitteltherapie, 2nd ed., 1985 pp. 242 f. [NiK30]; Guideline for Clinical Trials of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) of 1997 "General Considerations for Clinical Trials - E8", at 3.1.3 [HLNK18]).

43 bb) The reasonable expectation of success required for the conduct of phase I clinical trials (cf. generally Federal Court of Justice, judgment of 16 April 2019 - X ZR 59/17, GRUR 2019, 1032 - Fulvestrant) resulted, on the one hand, from the IC50 value of 2 nM demonstrated for tadalafil by in vitro tests (NIK5/NiK4 p. 17 line 5 ff., Table 1).

44 The NIK5/NiK4 explicitly states that this value justifies the expectation that tadalafil as a PDE5 inhibitor could be effectively suitable for the treatment of erectile dysfunction (NIK5/NiK4 p. 17 line 25 ff.: "The above data demonstrates the ability of the subject compounds of the invention to inhibit cGMP PDE, and hence their utility in the treatment of erectile dysfunction substantially as hereinbefore described.").

45 This is especially true in light of the fact that the IC50 value for sildenafil, the only PDE5 inhibitor known to date, was reported to be 3.9 +/- 0.9 nM and 3.0 to 3.6 nM, respectively (Boolell et al., Sildenafil: An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction, International Journal of Impotence Research 1996, 47, 50, l. Spalte, Table 2: "0.0039 µM" = 3.9 nM [NiK5]; Terret et al., Sildenafil (Viagra™), a potent and selective of type 5 CGMP phosphodiesterase with utility for the treatment of male erectile dysfunction, Bioorganic & Medical Chemistry Letters, 1996, 1819, 1822, Figure 5: "IC50 (nM), PDE5 ... 3.6 [platelet] - 3.0 [corpus cavernosum]" [HLNK8]), and thus at least 33% higher than the IC50 value of tadalafil.

46 The resulting expectation of success is not precluded by the fact that the IC50 value given in NIK5/NiK4 is based on in vitro tests. In principle, it cannot be ruled out that subsequent in vivo studies may result in different IC50 values (see the expert statements in the invalidity proceedings before the High Court of Justice of England and Wales: Dr. J. B. Saoud of 16 May 2016, marginal no. 4.1.2 [HLNK16]; Dr. G. B. Brock of 14 April 2017, marginal no. 5.28 [HLNK17]. However, the question of whether such deviations arise can only be answered after in vivo studies have been performed. For the selection of suitable candidates, the results of in vitro investigations are a suitable reference point. It is therefore irrelevant that the IC50 values for tadalafil given in NIK5/NiK4, which are based on in vitro tests, were not measured under identical analytical

conditions as the IC50 values for sildenafil, which are based on in vivo tests (see Bischoff, Potency, selectivity and consequences of nonselectivity of PDE inhibition, International Journal of Impotence Research 2004, 11, r. sp, last para., last full sentence [HLNK55]).

47 cc) Furthermore, it contributed to the reasonable expectation of success that in NIK5/NiK4 reference was made to the high selectivity of the compounds disclosed therein - and thus also of tadalafil - for PDE5 enzymes, as had been shown by standard studies (NIK5/NiK4, p. 16, line 24 transitioning to p. 17 lines 1f.).

48 dd) This was reinforced, as the Patent Court rightly stated, by the fact that NIK5/NiK4 already provided various formulation examples for the skilled person, i.e. already showed concrete ways of possible administration.

49 ee) Finally, the considerable financial success of sildenafil also contributed to the reasonable expectation of success (cf. Keith, The Economics of Viagra, Health Affairs 2000, 147, 148 [NiK29]), which made it appear very attractive from an economic point of view to provide a further PDE5 inhibitor with improved properties.

50 c) After conducting clinical trials on the tolerability of tadalafil in phase I clinical trials, the skilled person had to deal with the conceptual design of clinical trials on efficacy and dose-response relationships in phase II. Contrary to the opinion of the appeal, the skilled person had reason, based on NIK5/NiK4, to consider the daily oral administration of tadalafil independent of demand, in addition to the oral administration on demand.

51 aa) The Defendant correctly points out that sildenafil, as the only available PDE5 inhibitor at the time, was administered solely on demand in the Phase II clinical trials (NiK6, para. 1; NIK9, Goldstein et al., Oral Sildenafil in the Treatment of Erectile Dysfunction, The New England Journal of Medicine 1998, 1397, l. sp., para. 1: "... adminstered as needed ..."; NiK5, 47, 49, l. sp., last para.). Contrary to the defendant, however, this did not lead the skilled person to consider administration as needed alone also for tadalafil for the phase II clinical trials.

52 For the skilled pseron was at the same time aware that the need-based administration has its reason in the fact that sildenafil is not only very quickly absorbed by the human organism and reaches its highest concentration in the plasma about one hour after administration, but also in the fact that the half-life is only 3 to 5 hours (NiK5, 47, 50, para. 3).

53 Against this background, when the skilled person routinely determined the half-life of tadalafil at the start of Phase II, he found that it was approximately 17.5 hours and thus the effect of tadalafil lasted significantly longer in the patient than that of sildenafil (cf. Birss, J. in [2017] EWHC 1955 para 289 (Pat) - Actavis Group PTC EHF/TEVA UK Limited [HLNK26]; Kitchin, LJ. in [2017] EWCA Civ 1671 para 113 - Actavis Group PTC EHF/TEVA UK Li-mited; expert opinion G.J. Muirhead of 9 January 2020, p. 2 last para [NiK12]). This gave the skilled person reason to consider, in addition to oral administration as needed in the phase II clinical trials (possibly taking into account sleep times), daily oral administration of tadalafil independent of need.

54 bb) This approach was supported by the fact that the low IC50 value of tadalafil known from NIK5/NiK4, which the expert might have checked again by his own in vitro investigations before carrying out the comparatively complex clinical investigations in phase II (cf. Birss, J. and Kitchin, LJ., op. cit.), made it appear possible that, in the case of administration independent of need, even a low dosage of tadalafil with low side effects is still sufficiently effective.

55 cc) The inclusion of the administration of tadalafil independent of need was not decisively opposed by the fact that the clinical studies of phase II became more extensive and thus also more cost-intensive. On the other hand, the prospect of a PDE5 inhibitor as an alternative to the commercially very successful sildenafil, which was justified with regard to the aforementioned aspects, stood in contrast to this.

56 d) Based on NIK5/NiK4, the skilled person was also prompted to test the efficacy and tolerability of a demand-independent daily oral administration of tadalafil in a dosage of 5 mg in the clinical trials to be carried out, which made the subject-matter of patent claim 1 according to the main application obvious to him.

57 aa) However, a reason for carrying out such clinical investigations did not yet result from the dosage range of 0.5 to 800 mg disclosed in NIK5/NiK4 as generally being considered.

58 As the Patent Court has already correctly stated, this dosage range is so wide that, from a technical point of view, it cannot describe a therapeutically effective dosage regime. This assessment is consistent with that of the experts Dr. Brock and Dr. Saoud in the proceedings before the High Court of England and Wales (HLNK17 para. 10.2 and HLNK16 para. 4.2). It is also consistent with the further statements in NIK5/NiK4 that in practice the physician would determine the actual dosing regime according to the age, weight and reaction of the individual patient (NIK5/NiK4 p. 5 para. 1).

59 bb) For the skilled person, on the other hand, there was also no suggestion in NIK5/NiK4 to be guided solely by the value of 50 mg mentioned in connection with all formulation examples.

60 As already stated by the Patent Court, these are merely examples of how the active ingredient tadalafil can in principle be formulated. In contrast, there is nothing to indicate that the indicated value is already the result of dose-finding tests with several different dosages, as they usually take place in Phase II.

61 Precisely because no concrete data on differences between different dosages were available, the skilled pseron had reason to conduct the studies on do-sis-effect and side-effect relationships typical for phase II and, in a modified form, also for phase III.

62 cc) Whether the skilled person had reason to use dosage approaches that had been used in clinical studies of sildenafil, as the Patent Court stated, can remain undecided.

63 The selection of dosages of 5, 25, 50, and 100 mg, as cited in the early clinical trial of sildenafil disclosed in NiK6 (NiK6, Abstract 356; see also the selection of dosages of 10, 25, and 50 mg in another early trial in NiK5, p. 51, under "Clinical efficacy" and Figure 4), might be argued against by the fact that sildenafil was studied in later clinical trials only at the three higher dosages and that these higher dosages were associated with significantly higher efficacy

(Goldstein et al., Oral Sildenafil in the Treatment of Erectile Dysfunction, The New England Journal of Medicine 1998, 1397, 1399 l. Sp. under "Efficacy" and Table 2; expert opinion of Prof. Goldstein, HLNK22, 4. and 5.). The higher IC50 value of tadalafil determined in in vitro tests did establish a certain probability that this active ingredient also exhibits the intended level of efficacy in lower dosages. Nevertheless, it did not follow without further ado that the deviation of about 33% from the IC50 value determined for sildenafil gave sufficient reason to set the lowest dosage for tadalafil at 80% lower than the lowest dosage of sildenafil used in the later trials.

64 dd) Reason to consider a dosage of 5 mg, however, arose for the expert in any case from the fact that tadalafil, when administered daily, exhibits an effect plateau that extends at least up to a range of 10 mg (also: Birss, J., loc.cit. para. 343 iv; Kitchin, LJ., loc.cit. para. 140 f., Floyd, LJ., loc.cit. para. 169 f.; Lord Hodge in UK Supreme Court ([2019] UKSC 15 para. 84 ff - Actavis Group PTC EHF v ICOS Corporation [HLNK41 = NIK10]).

65 (1) Taking into account also the dose selection in the later clinical trials of sildenafil (NIK9, 1397 l. Sp.; 199 l. Sp., table 1) it is assumed that the skilled person would have carried out a first clinical investigation in phase II with dosages of 25, 50 and 100 mg of the active substance in order to determine the dose-response relationship of tadalafil or would have continued with this in any case in a second clinical investigation, it would have resulted from this that there is a plateau of effect in the range between 25 and 100 mg and this irrespective of whether the administration was carried out according to need or independent of need.

66 (2) This would have led the skilled person, according to good professional practice, to find out in further clinical investigations where the beginning of the effect plateau and thus a favorable relationship between the administered amount of tadalafil and its effect as a PDE5 inhibitor lies, taking into account undesirable side effects.

67 According to ICH guideline E4, the assessment of dose response is not only an integral part of drug efficacy. Rather, it is also recommended that further studies be conducted to determine the lowest effective dosage (ICH

Harmonised Tripartite Guideline "Dose-Response Information to Support Drug Registration - E4", p. 3, para. 4 under "Dose-Response Assessment Should Be an Integral Part of Drug Development"; p. 4, para. 3 under "Regulatory Considerations when Dose-Response Data are imperfect"; p. 6, para. 6 [HLNK19]). Accordingly, the Defendant's expert Prof. F. states that the complete characterization of dose-response relationships and the determination of the minimum effective dose are often meaningful components of the required clinical trial program to obtain drug approval (HLNK49, p. 3, para. 4 under Summary Conclusion).

68 (3) It may well be that after the clinical trials of 25, 50 and 100 mg, the skilled person would initially have included only a further dosage of 10 mg tadalafil in the further trials and from this it would have emerged for him that when tadalafil is administered as required, there is a considerable drop in efficacy between dosages of 10 and 25 mg. In this respect, reference is made to a diagram in the defendant's reply, in which the course of the effect curves as a function of the dosages is reproduced based on corresponding information in the patent specification (paragraph 81 f.) (reply, p. 37).

69 It is also not necessary to make a final decision as to whether the skilled person, notwithstanding this decrease in effect (for example, in IIEF question 3, of the patients who had taken dosages of 25 mg tadalafil, 83.7% still considered the penetration ability to be almost always or always given, whereas this was only the case in 48.8% of the patients who had taken dosages of 10 mg, cf. Contested patent specification marginal 81) considered the absolute efficacy values in the patients who had taken only 10 mg of tadalafil to still be interesting and was already therefore motivated to continue the clinical investigations also with an administration as required of 5 mg of the active ingredient, as claimed by the plaintiffs.

70 For irrespective of the answer to this question, the aforementioned drop in efficacy with on-demand administration of tadalafil would in any case not have deterred the skilled person from further investigations into the dose-response relationship with on-demand administration of tadalafil of less than 10 mg. At least with this type of administration, a drop in effect between dosages of 10 and 25 mg cannot be determined (cf. expert opinion of Prof. Dr. Porst, p. 2, para. 6

[HLNK45]), which is why the skilled pseron - following the recommendations of the ICH guideline E4 - was still obliged to test tadalafil in a dosage of 5 mg when administered as needed in order to determine the lower limit of the effect plateau.

71 (4) For the decision of the dispute, it is not relevant whether the complete characterization of the dose-response relationships was already mandatory in the clinical trial program for obtaining the drug approval (denying Prof. Fuhr, HLNK 49, p. 3 para. 4) or whether, in view of the great economic incentive, the skilled person had reason to conduct such studies only after market launch (cf. the expert statement of Dr. J. B. Saoud of May 16, 2016, marginal no. 3.19; ICH Harmonised Tripartite Guideline "General Considerations for Clinical Trials E8" marginal no. 3.1.3.2 para. 3 [HLNK18]).

72 Even if the latter were to be affirmed, the assessment of inventive step depends solely on whether there was already a reason for the skilled person on the priority date to conduct complete studies on the dose-response relationship at any time, possibly also at a later date. Such a reason follows in the case of dispute, as explained, from the fact that such studies - if necessary also only after market launch according to the recommendations of the ICH guideline E4 - correspond to good practice.

73 (5) The fact that an efficacy with lower side effects than sildenafil even with a daily oral administration of 5 mg was possibly surprising for the skilled person, as the Patent Court has rightly pointed out, also does not lead to a different assessment against the background shown.

74 According to the case law of the Senate, a technical teaching which has an effect that would not be expected from a certain starting point is nevertheless obvious to the skilled person if it appears as an obvious solution from another perspective. In such constellations, the surprising effect is to be regarded as a mere bonus effect which cannot lead to an affirmation of the inventive step (settled case law, see for example Federal Court of Justice, judgment of 15 April 2010 - Xa ZR 26/08, GRUR 2010, 607 marginal no. 80 - Fatty acid composition; judgment of 17 September 2019 - X ZR 71/17 marginal no. 68 - Dexmedetomidine).

75 From this point of view, it is also irrelevant whether the daily oral administration of tadalafil in a low dosage of 5 mg, independent of need, represented a significant change ("a clear paradigm shift") from a medical point of view compared to the then established on-demand medication with sildenafil in higher dosages of 25, 50 or 100 mg (cf. expert opinion Prof. Dr. Kliesch of November 5, 2019, p. 10, para. 2 [HLNK42]).

76 The Court of Appeal of England and Wales and the UK Supreme Court (Lord Hodge, para. 84 ff.; Kitchin, LJ. para. 146 ff.; Floyd, LJ. Rn. 169 et seq.; Lewison, LJ. para. 180) as well as the Gerechtshof Den Haag (judgment of 27 August 2019 - 200.244.921/01 para. 4.16 f. [NiK11]).

77 The Senate cannot agree with the divergent opinions of the Finnish Market Court (judgment of 15 June 2018 - A-49-17 [HLNK53]), the Danish Maritime and Commercial Court (judgment of 25 March 2019 - 131/19 [HLNK50]) and the President of the Czech Industrial Property Office (decision of 26 July 2018 - PV 2001-3879 [HLNK52]). In these decisions, the inventive step is essentially affirmed with the consideration that for the skilled person, the expectation did not arise that tadalafil already exhibits the favorable properties in question at a dosage of 5 mg. For the reasons stated above, this aspect is precisely not decisive for the legal assessment.

78 e) The use of a unit dose of 1 to 5 mg tadalafil protected by patent claim 10 was also obvious to the skilled person for the reasons stated. This applies irrespective of whether an on-demand administration alone was suitable for sildenafil.

79 f) With the exception of claims 3 and 7, which will be dealt with separately below, no independent inventive content of the patent claims referring back to claims 1 and 10 has been asserted or is otherwise apparent.

80 4. The subject-matter defended by auxiliary request I is broader than the subject-matter defended by the main request and therefore a fortiori not patentable.

81 5. Insofar as the defendant continues to defend alternatively patent claims 3 and 7 in the version of the main request (auxiliary requests I a and I b), patentability is also lacking.

82 a) Patent claim 3 differs from patent claim 1 in the version of the main request in that the latter exclusively comprises 5 mg of the compound in unit dose form. As can be seen from the explanations of the main request, such a limited subject-matter was also obvious to the skilled person from the state of the art.

83 b) The same applies with regard to patent claim 7 which, in comparison with patent claim 1 in the version of the main application, has the further feature that the dose form serves for use in treating a sexual dysfunction. Such a use was disclosed to the skilled person in NIK5/NiK4.

84 6. The subject-matter defended by auxiliary request II was also obvious to the skilled person from the state of the art.

85 a) It differs from auxiliary request I in that feature 4 is amended as follows and feature 6 is added:

> 4. ~~Die Einheitsdosisform ist geeignet~~ zur oralen Verabreichung (~~said unit dosage form is suitable~~ for oral administration).
>
> 6. zur Verwendung bei der Behandlung sexueller Dysfunktion (for use in treating a sexual dysfunction).

86 b) As the Patent Court correctly pointed out, the omission of the wording "the unitary form is suitable" in feature 4 does not lead to a relevant amendment of the subject-matter. Feature 6 is known from NIK5/NiK4, so that the subject-matter claimed by auxiliary request II was also obvious for the reasons stated in connection with the main request.

87 7. The assessment of the subject-matter defended by auxiliary request III also leads to the same result.

88 a) It differs from auxiliary request II in that feature 4 reads as follows:

89 4. for daily oral administration for daily oral administration.

90 b) The additional feature of daily administration was suggested to the skilled person for the reasons already explained in connection with the main application.

91 IV. The decision on costs is based on Sec. 121(2) Patent Act and Sec. 97(1) Code of Civil Procedure.

Bacher Grabinski Deichfuß

Rombach Rensen

Previous instance:
Federal Patent Court, judgment of 24 October 2017 – 3 Ni 22/15 (EP) connected with 3 Ni 27/15 (EP) -