Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2019-04-16
Docket Number / Aktenzeichen:	X ZR 59/17
Name of Decision / Name der Entscheidung:	Fulvestrant

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 59/17

Pronounced on:
16 April 2019
Zöller
Judicial Secretary
as Clerk of the
Court Registry

in the patent nullity proceedings

Fulvestrant

EPC Art. 56; Patent Act Sec. 4

a) Whether it is obvious for the skilled person to follow a solution path may also depend on the associated expectation of success. The requirements for a reasonable expectation of success cannot be formulated in a generally valid manner, but must be determined on a case-by-case basis, taking into account the subject matter in question, the extent of the incentive for the skilled person, the effort required to pursue a certain approach and the alternatives that may be considered as well as their respective advantages and disadvantages (confirmation of Federal Court of Justice, judgment of 19 April 2016 - X ZR 148/11, GRUR 2016, 10. April 2016 - X ZR 148/11, GRUR 2016, 1027 - Zöliakiediagnoseverfahren; judgment of 15 May 2012 X ZR 98/09, GRUR 2012, 803 - Calcipotriol-Monohydrat; judgment of 10 September 2009 - Xa ZR 130/07, GRUR 2010, 123 - Escitalopram).

b) When developing a formulation for an active pharmaceutical ingredient for human use, it is generally not decisive whether the skilled person can expect to find a result suitable for a clinical trial. Rather, an appropriate expectation of success may result from the possibility of verifying the efficacy and tolerability of a formulation in an animal trial with sufficient predictive value for therapeutic use in humans.

Federal Court of Justice, judgment of 16 April 2019 – X ZR 59/17 – Federal Patent Court

ECLI:DE:BGH:2019:160419UXZR59.17.0

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 16 April 2019, attended by the presiding judge Prof. Dr. Meier-Beck, the judges Gröning and Dr. Grabinski and the judges Dr. Kober-Dehm and Dr. Marx

ruled that:

> The appeal against the judgment of the 3rd Senate (Nullity Senate) of the Federal Patent Court of 12 January 2017, is dismissed at the expense of the defendant.

By operation of law

Facts of the case:

1 The defendant is the owner of European patent 1 250 138 (patent in suit), which was granted with effect for the Federal Republic of Germany and was filed on 8 January 2001, claiming the priority of two British applications dated 10 January 2000, and 12 April 2000, and relates to a fulvestrant formulation. The patent in suit was maintained in opposition proceedings before the European Patent Office in an amended version with 31 claims. In this version, patent claim 1 reads as follows:

> "Use of fulvestrant in the preparation of a pharmaceutical formulation for the treatment of a benign or malignant disease of the breast or reproduc-tive tract by intra-muscular administration, wherein the formulation com prises fulvestrant in a ricinoleate vehicle, a pharmaceutically acceptable non-aqueous ester solvent, and a pharmaceutically acceptable alcohol, and wherein the formulation is adapted for attaining a therapeutically significant blood plasma fulvestrant concentration for at least 2 weeks."

2 The applicants argued that the subject matter of the patent in suit was not patentable. Moreover, the patent in suit did not disclose the invention so clearly and completely that a skilled person could carry it out. The defendant defended the patent in suit as amended and, in the alternative, in six amended versions.

3 The Patent Court declared the patent in suit null and void. This is the subject of the defendant's appeal, which continues to defend the patent in suit

with its first-instance requests. According to auxiliary request IV, patent claims 1 and 2 are to be amended as follows:

> "1. Use of fulvestrant in the manufacture of a pharmaceutical formulation for the treatment of breast cancer by intramuscular administration to a human in need of such treatment, said formulation comprising dissolved fulvestrant, 10 weight percent ethanol, based on the volume of the formulation, 10 weight percent benzyl alcohol based on the volume of the formulation, 15 weight percent benzyl benzoate based on the volume of the formulation, and a sufficient amount of castor oil to produce a formulation containing at least 45 mgml-1 fulvestrant.
>
> 2. the use as claimed in claim 1, wherein the total amount of fulvestrant in the formulation is 250 mg and the total volume of the formulation is 5 ml."

4 The plaintiffs oppose the appeal.

Grounds of the decision:

5 The admissible appeal is unfounded; the Patent Court correctly found the subject matter of the patent in suit to be unpatentable.

6 I. The patent in suit relates to the use of 7α-[9-(4,4,5,5-pentafluoropentylsulfinyl)nonyl]estra-1,3,5(10)-triene-3,17β-diol or ICI 182 780 (international non-proprietary name: fulvestrant) in the manufacture of a pharmaceutical formulation for the treatment of benign and malignant diseases of the breast or reproductive tract.

7 According to the statements in the patent in suit, the treatment of many benign or malignant tumors in the breast or in the reproductive tract is essentially based on the withdrawal of estrogen. For this purpose, ovarian function is suppressed in pre-menopausal women by surgical or radiotherapeutic measures or by drug treatment, whereas aromatase inhibitors are used in post-menopausal women (ref. para. 2). An alternative approach to estrogen deprivation would be to antagonize estrogens with antiestrogens that competitively bind to estrogen receptors (ER). However, conventional non-steroidal antiestrogens such as tamoxifen are limited in their effect due to their partial agonism and do not completely block the estrogen-mediated activity of the cells (para. 3). This has prompted the search for new compounds that bind

with high affinity to estrogen receptors without triggering the regular hormonal response of estrogen, i.e., would be "pure" antiestrogen genes with the ability to completely block the trophic effect of estrogen. The first examples of such compounds were steroidal analogues of estradiol with an alkylsulfinyl side chain in position 7α. Among these, fulvestrant was of particular interest because of its pure antagonistic activity toward estrogen and its significantly higher antiestrogenic potency compared with other available antiestrogens.

8 Fulvestrant binds with a similar affinity to estrogen receptors as estradiol and completely blocks the growth-stimulating effect of estradiol on human breast cancer cells in vitro. It could therefore potentially offer improved therapeutic efficacy over tamoxifen. In healthy adult rats, maximum uterine involution can be achieved with a dose of fulvestrant that does not adversely affect bone density or increase gonadotrophin secretion. If this were also true in humans, these findings could be extremely important clinically (patent specifications para. 4-9).

9 A disadvantage of fulvestrant, however, is that, like other steroidal compounds, it has certain physical properties that make formulations with these compounds difficult. Compared to other steroidal compounds, fulvestrant is a particularly lipophilic molecule, and its solubility in water is extremely low (para. 11). Injectable steroidal sustained-release formulations were available on the market that used various oils as solvents, as well as additional excipients such as benzyl benzoate, benzyl alcohol, and ethanol, and achieved sustained release over periods of one to eight weeks. U.S. Patent Specification 5,183,814 (NiK43) described an oil-based fulvestrant formulation containing 50 mg fulvestrant, 400 mg benzyl alcohol, and a sufficient amount of castor oil to bring the solution to a volume of 1 ml. However, this formulation was too complicated for commercial-scale production because of the high alcohol concentration. As shown in Table 2 of the patent in suit and known for steroidal compounds, fulvestrant is significantly more soluble in castor oil than in other oils (paras. 14-16). However, even when castor oil is used, it is not possible to dissolve fulvestrant in an oil-based carrier alone in such a way that a sufficiently high concentration of the active ingredient is obtained at the maximum recommended

volume of 5 ml for an intramuscular injection and a therapeutically significant release rate is achieved (patent specifications para. 17-18).

10 2. The description of the patent in suit does not explicitly state which technical problem the patent in suit concerns. Against the background of the explanations in the disputed patent specification concerning the physical properties of fulvestrant, the concentration of the active ingredient required to achieve a significant therapeutic effect and the size of an injection volume that can be administered intramuscularly, the task of the disputed patent can be seen with the Patent Court in describing a use of fulvestrant suitable for the formulation of a medicament for the treatment of benign or malignant tumors in the breast or in the reproductive tract, with which the tolerability and the efficacy of the formulation are improved. Contrary to Defendant's view, this definition does not ignore that depot effect of the claimed fulvestrant formulation is also sought. The depot effect is an aspect of the effectiveness of the formulation and is thus included in the definition of the task derived by the Patent Court from the explanations in the patent specification in suit.

11 3. In order to solve this problem, the patent in suit, in the version of the patent claims in force and defended by the defendant with the main request, proposes a use of fulvestrant in the preparation of a pharmaceutical formulation for the treatment of a benign or malignant disease of the breast or of the reproductive tract, the further constituents of which are mentioned in claim 1 in general terms and without specifying the quantitative ratios, while in claims 2, 4, 18, 19, 23 and 24 adjoining claim 1 and in the sets of claims put forward in the alternative for decision, the desired fulvestrant concentration as well as the further constituents of the formulation are specified in terms of further components of the formulation are specified with respect to type and amount. are specified.

12 All features of the use according to the invention, which are at the center of the discussion of the parties in the appeal proceedings, result from patent claims 1 and 2 of auxiliary request IV. Accordingly, these can be divided as follows:

1. fulvestrant is used in the preparation of a pharmaceutical formulation for the treatment of breast cancer.
2. the formulation is intended for intramuscular administration.
3. the formulation contains:
   - 3.1 dissolved fulvestrant,
   - 3.2 10 percent ethanol by weight,
   - 3.3 10 percent benzyl alcohol by weight; and
   - 3.4 15 percent benzyl benzoate by weight, each based on the volume of the formulation,
   - 3.5 and castor oil,
   - 3.6 in an amount sufficient to produce a formulation containing at least 45 mgml-1 fulvestrant.
4. the total amount of fulvestrant in the formulation is. 250 mg.
5. the total volume of the formulation is 5 ml.

13 4. The description explains that the introduction of a non-aqueous ester solvent (preferably benzyl benzoate) soluble in castor oil and an alcohol (preferably a combination of ethanol and benzyl alcohol [also known as phenylmethanol]) facilitates the solubilization of fulvestrant. This was surprising, since the solubility of fulvestrant in non-aqueous ester solvents was significantly lower than the solubility in an alcohol and in castor oil (para. 19).

14 II. The Patent Court gave the following main reasons for its decision:

15 It could be left open whether the subject-matter of the subordinate patent claims in the current version was disclosed in an executable manner and was new. In any case, it was not based on inventive step, since it was suggested to the skilled person, a pharmaceutical technologist (galenicist) with university education and several years of practical experience in the field of formulation of steroid compounds, working in a team with a physician specializing in gynecology, by the publications of Howell et al. (Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182 780 in women with advanced breast cancer, British Journal of Cancer (1996) 74, 300-308, NiK16) and by McLeskey et al. (Tamoxifen-resistant fibrolast

growth factor-transfected MCF-7 cells are crossresistant in vivo to the antioestrogen ICI 182 780 and two aromatase inhibitors, Clin. Cancer Res. 1998, pp. 697-711, NiK10).

16 NiK16 reported on a successful clinical study of the long-term efficacy and toxicity of fulvestrant in patients with advanced breast cancer, describing a castor oil-based formulation of fulvestrant that was administered intramuscularly once a month to patients participating in the study and thus had a sustained release effect. Since the formulation of the administered fulvestrant injection solution was not specified in detail in NiK16, the expert, in his search for a suitable formulation for the active ingredient fulvestrant, had reason to research whether formulations were known whose composition corresponded to that in NiK16, i.e. which were based on castor oil and contained 250 mg fulvestrant in 5 ml solution. In doing so, he had come across NiK10, which dealt with studies on tamofixen resistance in the treatment of breast cancer and indicated a fulvestrant formulation containing ethanol, benzyl alcohol and benzyl benzoate in addition to castor oil. Thus, the fulvestrant formulation of NiK10 comprises all the components mentioned as preferred by the patent in suit and thus, in combination with NiK16, suggests the subject matter of claim 1.

17 III. This assessment stands up to review in the appeal proceedings.

18 1. The Patent Court rightly considered the citation NiK16 as a plausible starting point for the skilled person when assessing the inventive step.

19 a) NiK16 reports on a study to investigate the long-term efficacy and toxicity of fulvestrant. Nineteen patients who had advanced breast cancer and had developed resistance to tamoxifen were selected for the study. The patients were injected with fulvestrant in the form of a castor oil-based formulation once per month in a 5 ml volume depot injection intramuscularly. The first four patients received a dose of 100 mg of the drug in the first month and, after local or systemic toxicity of the administered dose could be ruled out, a dose of 250 mg starting in the second month. The remaining patients were given a dose of 250 mg of fulvestrant per month from the beginning. Regarding the results of the study, NiK16 states that measurements of the concentration of fulvestrant showed that at both the 100 mg dose and the 250 mg dose, there was

continuous delivery of the active ingredient from the de-pot formulation over the one-month dosing interval, with peak levels reached on average eight to nine days after dosing, then decreasing, but still above the targeted therapeutic threshold on day 28. Thus, the targeted therapeutic concentration of fulvestrant, determined on the basis of previous animal studies and from a phase I study, could be maintained over a period of one month by means of a single intramuscular injection (NiK16 pp. 300 under "Summary," p. 302 under "Results - Pharmacokinetics," and p. 305 under "Discussion"). Side effects occurred only to a negligible extent and only in isolated cases. In contrast, none of the patients experienced serious side effects. In particular, the formulation administered did not lead to night sweats and hot flushes. Despite the relatively large administered volume of 5 ml, the formulation used was also well tolerated by most patients at the injection site (NiK16 p. 300 under "Summary," p. 303 under "Side-effects," and p. 305 under "Discussion"). 13 of the 19 patients (69%) had responded to treatment for a median duration of 25 months (NiK16 p. 300 under "Summary," p. 305 under "Response," and p. 306 under "Discussion").

20 b) Against this background, the assumption of the Patent Court that in the search for a suitable formulation for the active ingredient fulvestrant, the skilled person was prompted to examine whether a castor oil-based formulation corresponding to the one mentioned in NiK16 was known, withstands the attacks of the appeal.

21 aa) The appeal claims that the few properties of the formulation of fulvestrant investigated in the clinical study disclosed in NiK16 did not provide the skilled person with a basis on which he could have built to solve the task set. If the skilled person had attempted to develop a castor oil-based formulation containing 250 mg of fulvestrant in an injection volume of 5 ml himself, he would again not have been able to assume that it had the properties of the formulation described in NiK16. The patent in suit and the publication of Riffkin et al. (Castor Oil as a Vehicle for Parenteral Administration of Steroid Hormones, Journal of Pharmaceutical Sciences 1964, p. 891, NiK19) showed that the compatibility of the formulation depended strongly on the exact composition. However, NiK16 does not disclose the accompanying substances of the formulation. In addition, NiK16 describes not inconsiderable side effects, and the authors of the paper

themselves assumed that the reported results were only preliminary and that further studies were still required.

22 In partial agreement with this, the Technical Board of Appeal 3.3.01 of the European Patent Office assumed in its decision of 24 January 2019 (T 1680/17, HE52) that the skilled person would have been aware that the good local tolerability at the injection site reported in NiK16, referred to there as D4, could not be expected for any castor oil-based fulvestrant formulation. He noted clear evidence from the literature (NiK19) of side effects associated with specific formulations, and there was no reason to believe that the efficacy of the treatment was not similarly associated with the formulation (p. 27 at 5.2.3). This had direct implications for the correct formulation of the task (p. 28 on 5.2.4), which was to provide a castor oil-based vehicle for a fulvestrant composition that enabled breast cancer treatment by intramuscular injection (p. 30 on 5.3.3). It should therefore be examined, inter alia, whether the skilled person would have arrived at the formulation according to the invention in anticipation of a solution to the technical problem (p. 31 at 5.5). For this purpose, the Board of Appeal considers, on the one hand, the technical knowledge on steroid formulations based on castor oil, and on the other hand, because of the specific fulvestrant formulation mentioned therein, the citation NiK10 designated as D1. According to the Board of Appeal, the citations not dealing specifically with a castor oil-based fulvestrant formulation did not contain any information from which the skilled person could have learned how to solve the problem of the acknowledged difficulty of formulating fulvestrant. The skilled person would have used the formulation according to the invention mentioned in NiK10 if he had associated a reasonable expectation of success with it (p. 36 to 5.5.4). This was not the case, since the subject matter of the work was in the field of basic research and therapeutic applications were also referred to in NiK16 only in this context. A formulation in basic research is aimed at a high concentration at the desired site of action and does not require considerations of pharmacologically suitable concentration, safety and tolerability. Unlike commercially available steroid formulations for parenteral administration, the NiK10 formulation contained three cosolvents in addition to the base oil. The skilled person would therefore have had reservations about using the formulation in a clinical context and would have been wary of using a formulation with a combination of an

unusually high number of excipients in unusual concentrations in a clinical study (p. 36-41 on 5.5.5 and 5.5.6).

23 Finally, similar considerations underlie the decision of the Gerechtshof Den Haag of 27 November 2018 (200.237.828/01, HE47) and the expert judge opinion of the Swiss Federal Patent Court of 23 November 2018 (O2018_009, HE49), which, like the Board of Appeal, conclude that the subject matter of the patent in suit was therefore not obvious, and similar considerations are made in the declaration of Dr. S. McLeskey (HE1) and by the party expert of the defendant Dr. K. S. (HE5, HE6 and HE45).

24 bb) The Senate cannot agree with this.

25 (1) The reservations cited by the appeal against the strong incentive resulting from NiK16 to clarify the wording used in the clinical study do not prevail and are rightly not shared by the above-mentioned decisions, the expert judge's opinion of the Swiss Federal Patent Court and the expert opinions.

26 The writing discloses a formulation with the active ingredient fulvestrant, already known for the treatment of breast cancer, and with castor oil as carrier substance, which was known at the priority date as the most suitable oil-based solvent for fulvestrant, as also explained in the patent specification in dispute. Furthermore, in the study, the formulation was administered with the recommended injection volume of 5 ml for intramuscular administration and a depot effect was achieved over one month. This indicates a potential of the formulation used, which as the Patent Court rightly assumed - gave the skilled person reason to look for a formulation for fulvestrant with the same concentration as the formulation used in NiK16.

27 Without success, the appeal claims that the expert would not have pursued this approach because NiK16 described not insignificant side effects, the study was not representative in view of the small number of patients participating, and the authors of NiK16 themselves also considered further studies necessary to confirm the response rate and the long-term effects. It is already not true that the NiK16 study disclosed significant and undesirable side effects of fulvestrant. As the plaintiffs correctly point out, the side effects

described in NiK16, such as transient vaginal discharge or temporary changes in body odor or greasy hair, are to be seen in comparison to the severity of the disease to be treated and are therefore classified in NiK16 as only minor, so that it cannot be assumed that the skilled person was deterred by this from pursuing the development of a fulvestrant formulation on the basis of NiK16. On the contrary, it can be assumed that NiK16 appeared interesting to the expert as a starting point primarily because the study described showed that the severe impairments typically associated with treatment with tamoxifen, such as sweating and hot flushes, do not occur with the use of fulvestrant. Similarly, the number of patients studied for the study and the response rate of 69% could not have prevented the expert from taking up the suggestions from NiK16. The expert therefore had no reason to doubt that the authors of the study, as stated in the abstract, demonstrated with fulvestrant, when administered in the form of monthly depot injections at the concentration described, an active "second-line antiestrogen" with no discernible negative effects on the liver, brain or sex tract, whose further investigation in patients with advanced breast cancer was rewarding.

28 In particular, it is also irrelevant that the authors of NiK16 consider further investigations to be necessary. In this respect, the report on the clinical study clearly goes beyond the disclosure of the patent in suit. In the experimental part, the description is limited to investigations of the solubility of fulvestrant in different solvents as well as in mixtures of these agents and describes the efficacy of the claimed formulation only on the basis of results from experiments with eight rabbits (patent specifications para. 47 f.). This corresponds to the concern explained in the general description to find a suitable formulation for fulvestrant, which is known to be a potent active ingredient but is difficult to formulate, and which, as the patent in suit explains (ref. para. 9), could be highly relevant clinically if the results from the animal experiments could be transferred to humans. Since the patent in suit leaves this question open and must leave it open according to its empirical basis, however, no other requirements can be placed on the prior art in this respect.

29 (2) Against this background, the Senate does not share the assumption of the Technical Board of Appeal that an inventive step is to be

affirmed already because the skilled person could not have expected to find a fulvestrant formulation according to the prior art which could be suitable for a therapeutic application in humans.

30 a) The Board of Appeal opined that the skilled person should have had concerns about using the unusual formulation of NiK10 in a clinical trial. Even if this may be true, it is not relevant here.

31 (b) The requirements for the expectation of success cannot be formulated in a generally applicable manner, but must be determined on a case-by-case basis, taking into account the subject matter at issue, the extent of the incentive for the skilled person, the effort required to pursue a certain approach and the alternatives that may be considered, as well as their respective advantages and disadvantages (Federal Court of Justice, judgment of 19. April 2016 X ZR 148/11, GRUR 2016, 1027 marginal no. 22 Zöliakiediagnoseverfahren; judgment of 15 May 2012 X ZR 98/09, GRUR 2012, 803 marginal no. 46 - Calcipotriol-Monohydrat; judgment of 10 September 2009 Xa ZR 130/07, GRUR 2010, 123 marginal no. 38 et seq. Escitalopram).

32 The skilled person was aware that he could not immediately use a fulvestrant formulation found by whatever means in a clinical study if it had not already been used in such a study. Rather, he was required to test in animal studies whether the formulation was effective and tolerable. The requirements for the reasonable expectation of success must be based on the effort required for this. The fact that the therapeutic usability in humans and the efficacy and tolerability of this use must remain open is in the nature of things when developing a formulation for an active pharmaceutical ingredient.

33 (3) In view of this, the fact that a fulvestrant formulation based on castor oil, which was not described in detail with regard to the solvents used, had been successfully clinically tested in NiK16, provided a strong incentive for the skilled person to search for a solvent composition for which the efficacy and tolerability reported in NiK16 could at least initially be verified in animal studies.

34 2. Accordingly, the Patent Court also correctly assumed that the skilled person had reason to use the castor oil-based fulvestrant formulation disclosed in NiK10 for corresponding tests.

35 a) In addition to a fulvestrant formulation based on peanut oil, NiK10 also describes a fulvestrant formulation based on castor oil with an active ingredient concentration of 50 mg/ml containing 10% ethanol, 15% benzyl benzoate and 10% benzyl alcohol (NiK10 p. 698 r. sp., penultimate paragraph). This formulation was reported by the authors to have been used by Z. P. for the tests described in NiK10, which were intended to investigate whether the development of resistance to this agent observed after initially successful treatment of breast cancer with the standard drug tamoxifen was due to the fact that the cellular effects mediated by the fibroblast growth factor (FGF) receptor occur independently of estrogen receptor activation (NiK10 p. 697 "Abstract"). To do this, it was necessary to exclude any influence of estrogens on cancer cell growth. To this end, FGF-expressing human MCF-7 breast cancer cells resistant to tamoxifen were implanted into mice after they had previously had their ovaries removed to prevent the activation of estrogen receptors by endogenous estrogen. Since even ovariectomized mice still produce small amounts of estrogen, the aim was also to prevent possible stimulation of tumor growth by these estrogens. For this purpose, the experimental animals were subcutaneously injected with one of the two fulvestrant formulations described in NiK10 with a volume of 1 ml once a week (NiK10 p. 698 "Materials and Methods"). The experiments revealed that fulvestrant does not inhibit estrogen-independent tumor growth and consequently mediates an alternative growth signal via the fibroblast growth factor (FGF) receptor that is independent of estrogen receptor activation and is unresponsive to treatment with antiestrogens such as tamoxifen or fulvestrant (p. 700 "Results").

36 b) Contrary to the opinion of the appeal, consideration of NiK10 is not ruled out simply because the expert would not have found NiK10 during a search. The test report was published in March 1998 and thus almost two years before the priority date in a relevant scientific journal ("Clinical Cancer Research"). Thus, as also assumed by the Technical Board of Appeal, the Hague Court of Appeal and the expert judge, it belongs without further ado to

the relevant prior art. The fact that NiK10 may not yet have been available in a full-text form that can be searched electronically via the Internet before the priority date is irrelevant for legal reasons.

37 c) The expert also had no reason, contrary to the defendant's assertion, to disregardNiK10 because the reported trials were not designed to investigate the efficacy of fulvestrant in treating a breast cancer patient, but rather the fulvestrant formulation was used merely as a tool to determine a possible cause of resistance of some breast cancer patients to the standard treatment drug tamoxifen. NiK10 showed the skilled person, as will be explained in more detail below, that the castor oil-based fulvestrant formulation described therein could in any case suppress the production of estrogen, which, as the patent in suit also explains, was already considered essential at the priority date for the treatment of cancers of the breast and reproductive tract.

38 d) Contrary to the view of the defendant, the skilled person could also associate an appropriate expectation of success with the use of the fulvestrant formulation described.

39 aa) As stated, it was not directed to suitability for a clinical trial, but (initially) to verify the assumed efficacy and tolerability in animal experiments, as in the rabbit test described in the patent in suit.

40 bb) It is true that the experimental design of NiK10 shows that fulvestrant does not inhibit estrogen-independent tumor growth, i.e. tumor growth not stimulated by estrogen, and is thus indeed not suitable for the treatment of such tumors. Meanwhile, NiK10 confirms the efficacy of fulvestrant in the treatment of estrogen-dependent tumors with reference to the NiK16 study (NiK10 p. 698 li. sp. Z. 5 and footnote 19). In addition, the authors of NiK10 substantiate the anti-estrogenic effect of fulvestrant with a control experiment that they performed after fulvestrant had been shown to have no effect against estrogen-independent tumors. The experiment was designed to test whether fulvestrant was nevertheless active with respect to endogenous estrogens and prevented their effect on the uterus. For this purpose, healthy reproductive mice were injected for two weeks with the same dose of fulvestrant as the mice infected with cancer cells. Since the uterus of these mice weighed less than

untreated mice at the end of the experiment and had no endometrial glandular structure (NiK10 pp. 701/702), there was evidence that fulvestrant had remained effective as an antiestrogen. Uterine weight determination is a standard method for evaluating the effect of estrogens and antiestrogens, to which the patent in suit also refers in paragraph 9 of the specification (cf. expert opinion Prof. Dr. A. B. [NiK30], p. 4 bottom/5 top). The expert could therefore assume that fulvestrant in the formulation administered in the tests of NiK10 acts as an antiestrogen and was therefore fundamentally suitable for the treatment of estrogen-dependent tumor growth, as was already known to him from NiK16. The objection of the defendant that it was not clear from NiK10 whether the uterus test had been carried out with the peanut oil-based or with the castor oil-based Fulvestrant formulation, so that the skilled person could not have drawn any conclusions with regard to the effect of a castor oil-based Fulvestrant formulation, is not valid. Since the uterus test was a control experiment, it could be assumed, in the absence of indications to the contrary, that the same formulations were used as in the initial experiments and, in particular, that the castor oil-based formulation was also tested for its antiestrogenic effect.

41 cc) Contrary to the view of the defendant, the skilled person would also not have disregarded NiK10 because the results there were based solely on experiments in mice and subcutaneous administration and he would therefore not have expected that the formulation described in NiK10 would also be suitable for use in humans and, in the dosage administered in the animal studies, would develop an antiestrogenic effect in humans when administered in the manner described in NiK16 (intramuscularly instead of subcutaneously) and at the intervals specified therein (once a month) and would prove to be tolerable.

42 (1) The dose and active substance concentration required for the treatment of breast cancer was already known to the expert from NiK16.

43 (2) The castor oil-based fulvestrant formulation disclosed in NiK10 contains benzyl benzoate, benzyl alcohol and ethanol, which are also known to the skilled person from steroid formulations that can be administered intramuscularly (cf. Expert Opinion I. , Annex A, p. 1, HE36). Against this background, the expert had no reason not to consider the formulation from

NiK10 because it had been administered subcutaneously. Moreover, it was part of the general expert knowledge that the same provisos apply to intramuscular injection as to subcutaneous injection and that there are no differences in principle between the two modes of administration with regard to the resorption ratios (Karzel/Liedtke, Allgemeine Pharmako-logie, 1977, Chapter 5.5., NiK36). The Defendant's party expert also assumes that when developing a formulation, the study of pharmacokinetics in a suitable animal model (usually mouse or rat) is followed by a review of the initial animal experiments "in a 'closer-to-human' test animal (e.g., rabbit, if, for example, intramuscular administration is intended)" (cf. party expert opinion Dr. K. S., HE6, p. 4). However, this presupposes that the effect of subcutaneous administration in mice or rats is attributed a predictive value for the effect of intramuscular administration in rabbits, which is generally preferred in particular for lipophilic depot preparations (cf. party expert opinion Prof. Dr. C.-M. L. , NiK27, marginal no. 21) (just as it is for the effect of intramuscular administration in humans). The expert judge's opinion for the Swiss Federal Patent Court also assumes this (HE49, p. 12 f.). This is confirmed by the LASA Good Practice Guidelines, according to which subcutaneous administration is recommended for small laboratory animals and corresponds to good professional practice, because intramuscular injection can be difficult here due to the lack of large muscles (NiK21 under C).

44 (3) The different administration intervals in NiK16 (once a month) and in NiK10 (once a week) could also not lead the skilled person to the assumption that the fulvestrant formulation of NiK10 was unsuitable for the application described in NiK16. He was aware from NiK16 that an active substance concentration of 50 mg/ml with ri-zinus oil as carrier substance has a depot effect lasting one month. He could therefore assume that the active ingredient concentration and the type of carrier substance are decisive for the long-term effect, especially since the expert was also aware from other publications that steroid hormones in oil solutions, especially in castor oil, have a longer effect (cf. NiK19 p. 891 r. sp. overlapping paragraph to p. 892 l. sp.). Since these factors are identical in NiK16 and NiK10, the shorter administration interval in NiK10 provided no reason not to consider the formulation disclosed in NiK10 for the purposes of NiK16.

45 (4) Also as far as the defendant claims that the skilled person would not have included the fulvestrant formulation from NiK10 in his considerations already because of the benzyl alcohol content of 10%, because for example it was known from the publication NiK19 that an increase in the concentration of benzyl alcohol from 2% to 5% leads to a significant increase of local irritations, this cannot be accepted.

46 The skilled person could learn from NiK19 that even when steroids are dissolved in castor oil, further auxiliaries are necessary to dissolve the higher concentrations required for therapeutic treatments. In this context, NiK19 mentions benzyl alcohol and benzyl benzoate, which the authors of NiK19 attribute, in addition to improving solubility, the further advantage of facilitating injection of the formulation (NiK19 p. 893/894). Accordingly, there was no reason to regard the formulation disclosed in NiK10 as unsuitable from the outset, especially since, in view of the severity of the disease to be treated, irritation at the injection site is of secondary importance. This is also the opinion of the expert judge for the Swiss Federal Patent Court (HE49, p. 13).

47 The same applies to the unusual combination of three cosolvents cited by the Technical Board of Appeal. On the contrary, the known difficulty of solubilization of fulvestrant, also cited in the patent in suit, gave the skilled person reason to examine whether this combination of cosolvents, unusual at first glance, might not be the key to formulating an effective and tolerable castor oil-based fulvestrant composition, as had been successfully used in a clinical study in NiK16.

48 (5) Finally, the fact that in NiK10 it is not indicated whether the percentages are percentages by weight or percentages by volume could also prevent the skilled person from considering the disclosed formulation; in this respect, reference can be made to the correct explanations in the judgment under appeal as well as to the expert judge's opinion for the Swiss Federal Patent Court (HE49, p. 14).

49 3. Against this background, the subject-matter of the patent in suit, both in the valid version defended by the main request and in the versions

defended by the auxiliary requests Ia and Ib and II to IV, was made obvious to the skilled person by the citations NiK16 and NiK10.

50 4. Nothing else applies to the subject-matter of patent claim 1 in the version defended by auxiliary claim V, in which the features of auxiliary claims Ia and IIb are combined and it is added as a further feature that the formulation is adapted to achieve a therapeutically significant fulvestrant concentration in blood plasma of at least 8.5 ngml-1 for at least two weeks. NiK16 gives 10.5 to 12.8 ngml-1 as the maximum values for the blood plasma concentration of fulvestrant and 3.1 to 5.6 ngml-1 as the minimum values one month after application. As stated above, based on NiK16, the skilled person had reason to further investigate the castor oil-based fulvestrant formulation disclosed in NiK10 and to use it for testing. In doing so, he also achieved a blood plasma concentration that lies within the range disclosed in NiK16, in which the claimed lower limit of 8.5 ngml-1 also falls. The skilled person was therefore able to arrive at the subject-matter of patent claim 1 in the version defended by auxiliary request V on the basis of NiK16 and NiK10 without any inventive step.

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

Meier-Beck Gröning Grabinski

Judge at the Federal Court of Justice Dr. Marx cannot sign due to absence on vacation.

Kober-Dehm Meier-Beck

Previous instance:
Federal Patent Court, judgment of 12 January 2017 – 3 Ni 17/15 (EP) connected with 3 Ni 18/15 (EP) -