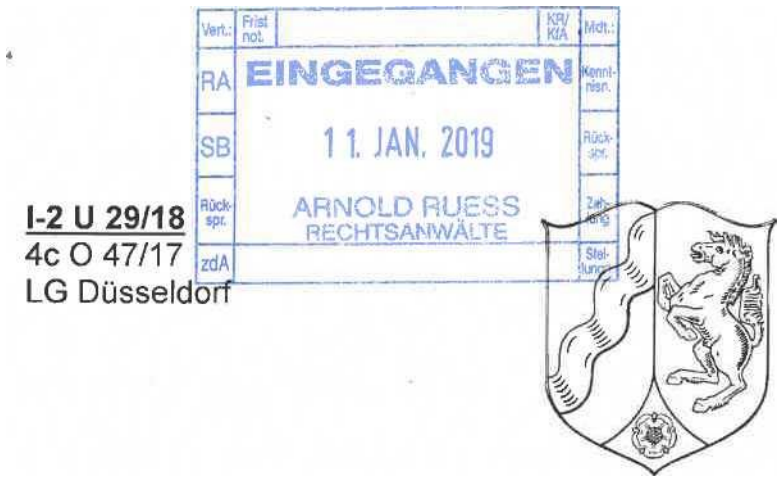

Pronounced on 09 January 2019
Krüger,

Judicial Officer

As Clerk of the Court

HIGHER REGIONAL COURT DÜSSELDORF
IN THE NAME OF THE PEOPLE
JUDGMENT

In the legal dispute

AstraZeneca AB, legally represented by its Vice-President, Mats Peter Berglund, 15185 Södertälje, Sweden,

Plaintiff and Appellant,

Attorneys of record: Lawyers Hoffmann Eitle in Munich,

vs.

Hexal AG, represented by its Directors, Dr. Andreas Eberhorn, Sandrine Piret-Gerard, Wolfgang Späth, Matthias Weber and Dieter Ziebold, Industriestraße 25, 83607 Holzkirchen, Germany

Defendant and Appellee

Attorneys of record: Rechtsanwälte Arnold Ruess in Düsseldorf,

Presiding Judge at the Higher Regional Court, Dr. Kühnen, and the Judges at the Higher Regional Court, Fricke and Thomas, the 2nd Civil Senate of the Higher Regional Court Düsseldorf, following the hearing on 09 January 2019, have

adjudged as follows:

I. The appeal against the judgment of Civil Chamber 4c of the Regional Court Düsseldorf, pronounced on 05 July 2018, is dismissed.

II. Plaintiff also bears the costs of the appeal proceedings.

III. This judgment and the Regional Court judgment are provisionally enforceable. Plaintiff may avert enforcement against security of 120% of the amount to be recovered unless Defendant furnished security in the same amount prior to enforcement.

IV. A further appeal is not allowed.

V. The value in dispute is assessed at € 1,500,000.

Grounds:

I.

Plaintiff is the registered proprietor of the German part of the European patent 1 272 195 B1, registered with the German Patent and Trade Mark Office under file number DE 601 13 975 T2. The patent in suit was filed on 02 April 2001 in English, claiming British priority on 05 April 2000; the reference to the patent grant was published on 12 October 2005. In opposition and opposition appeal proceedings, the patent in suit was maintained to the extent granted (decision of the Technical Board of Appeal of the EPO of 14 February 2013, Exhibits HE 4/HE 4a). The patent in suit currently is the subject of nullity proceedings pending before the Federal Patent Court, where a decision has yet to be handed down.

The patent in suit relates to the "use of fulvestrant in the treatment of resistant breast cancer"; its claim 1 states:

> *"Use of fulvestrant in the preparation of a medicament for the treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment."*

In the registered German translation, claim 1 states:

> "*Verwendung von Fulvestrant bei der Herstellung eines Arzneimittels zur Behandlung einer Brustkrebspatientin, bei der die vorangegangene Behandlung mit einem Aromataseinhibitor und Tamoxifen fehlschlug."*

In its complaint, Plaintiff challenges offering and placing of the medicinal product "Fulvestrant Hexal 250 ml injection solution in a pre-filled syringe" on the market for therapeutic use in the claimed group of patients. AstraZeneca UK is the holder of the marketing authorization for the reference medicinal product Faslodex®.

The challenged embodiment initially was listed in the Lauer Taxe [pharmaceutical database] on 15 December 2015. The "Patient leaflet: Information for Users" (Exhibit HE 6) includes the following note:

> *"Fulvestrant Hexal contains the active substance fulvestrant, which belongs to the group of estrogen blockers. Estrogens are female sex hormones and in certain cases can be involved in the growth of breast cancer.*
>
> *Fulvestrant Hexal is used to treat advanced or metastatic breast cancer in postmenopausal women."*

The published "Prescribing information" (Exhibit HE 7) states (in excerpts):

> *"4.1 Areas of application*
>
> *Fulvestrant HEXAL is indicated for the treatment of postmenopausal women with estrogen receptor positive, locally advanced and metastatic breast cancer with recurrence during or after adjuvant antiestrogen therapy or disease progression under treatment with an antiestrogen."*

After the sale of the challenged embodiment had been suspended in the meantime, following temporarily successful preliminary injunction proceedings, the challenged embodiment - after the prohibition orders had been lifted - has been listed again in the Lauer Taxe since 01 March 2017.

Plaintiff complains that Defendant's product at issue infringes the patent. It invokes a special evaluation of the mamma carcinoma tumor register carried out by iOMEDICO AG (Exhibit HE 8), with the database having a reference date of 31 October 2016 and which includes a total of 444 patients with HR-positive, locally advanced or metastatic breast cancer who have undergone fulvestrant-therapy in the 10-year period between 2007 and 2016. According to the table below, the patients had been pretreated with tamoxifen (hereinafter: Tam) and/or an aromatase inhibitor (hereinafter: AI):

Table 1 Endocrine pre-treatment of patients with fulvestrant-therapy

	2007-09[a]	2010-12	2013/14	2015/16[b]	Total
Patients (N)	174	129	89	52	444
pre-treatment with both Tam and AI (%)	50.0	51.2	34.8	36.5	45.7
both adjuvant (%)	17.2	27.1	16.9	34.6	22.1
one adjuvant, one palliative (%)	25.9	20.9	15.7	1.9	19.6
both palliative (%)	6.9	3.1	2.2	0.0	4.1
pre-treatment with either Tam or AI					
adjuvant or palliative (%)	44.3	37.2	50.6	36.5	42.6
no treatment with either TAM or AI documented					
adjuvant or palliative (%)	5.7	11.6	14.6	26.9	11.7

Tam: Tamoxifen I AI: Aromatase inhibitor
[a]The years refer to the commencement of therapy with fulvestrant. All documented instances of treatment with fulvestrant are shown, regardless of the treatment line.
[b]Recruitment at the start of the first-line therapy until June 2016. Documentation of higher therapy lines until data status 31 October 2016.

Since the patent in suit does not distinguish between palliative and adjuvant pre-treatment and since an adjuvant administration of tamoxifen as well as an aromatase inhibitor within the meaning of the patent in suit could also be considered to have "failed" in case of a subsequent recurrence of the breast cancer, all patients who have been pretreated - whether adjuvant or palliative - with tamoxifen and an aromatase inhibitor are deemed to be relevant (cf. brackets above).

In nearly half of the patients included in the evaluation (exactly: 45.7%), the facts thus were such that their pre-treatment with tamoxifen and an aromatase inhibitor is deemed to have failed and they subsequently were prescribed fulvestrant. Since the prescribing information for the challenged embodiment itself mentions only the pre-treatment with tamoxifen as an indication, the special evaluation is deemed to confirm that it is firmly established in medical and clinical practice to prescribe fulvestrant for use to a large extent if both pre-treatment with the antiestrogen

tamoxifen has failed and (further) pre-treatment with an aromatase inhibitor has also failed. Plaintiff is said to take advantage of that prescription practice and thus must be treated as if it had itself recommended the use of the active substance fulvestrant after the failed administration of tamoxifen and an aromatase inhibitor.

The Regional Court dismissed the complaint with the judgment under appeal. In the grounds of the judgment, it essentially stated: The admissible action has no merit. It is said that it is indeed possible to agree with Plaintiff's view that a failure of a previous breast cancer treatment with an aromatase inhibitor and tamoxifen is the case whenever the therapy initially carried out with the active substances in question was unsuccessful, which is not only the case with a palliative administration for the treatment of a manifest tumor, but likewise also if the pre-treatment with tamoxifen and an aromatase inhibitor was adjuvant, but turned out to be ineffective (and hence has "failed"), because the breast cancer returned nonetheless. It is also deemed possible to dispense with evident customizing if an actual prescription practice exists in the sense of protected use, which renders any further customizing unnecessary and which Defendant allegedly is utilizing. However, the demand for relief is said to fail as it is not possible to establish with the required reliability that the challenged embodiment is used to a sufficient extent in a palliative therapy following the failure of treatment with tamoxifen and failure of treatment with an aromatase inhibitor. The special evaluation of iOMEDICO AG submitted by Plaintiff is deemed unsuitable for proving the alleged scope of use. Neither did the evaluated figures appear sufficiently meaningful nor can it be ruled out that at the time of the hearing there had been any change in practical use with regard to novel CDK4/6 inhibitors that would be relevant for the decision.

This is addressed by Plaintiff's appeal, which Plaintiff substantiates primarily as follows: The Regional Court allegedly ignored the fact that Defendant denied the scope of the patented prescription practice only against the background of its incorrect interpretation of the patent, which was rightly rejected by the Regional Court, i.e. that only palliative pre-treatment is relevant, as it alone could "fail". Based on the correct, broad understanding of the patent in suit, the considerable scope of use of fulvestrant following (palliative or adjuvant) pre-treatment with tamoxifen and an aromatase inhibitor thus is deemed undisputed and does not need any further clarification in court. However, even if evidence were required, it would be sufficiently furnished by the submitted special evaluation. Since no better studies based on a broader database are available, the Regional Court is deemed to have exceeded the requirements of proof of a particular prescription practice. The use of novel CDK4/6 inhibitors is said to lack any legal significance because, according to the patent, a certain unsuccessful pre-treatment is required, while it is irrelevant whether fulvestrant is used as monotherapy or in combination with a CDK4/6 inhibitor.

Plaintiff request that

the Regional Court judgment be amended and

I. Defendant be ordered,

1. under penalty of a fine to be imposed, but not exceeding EUR 250,000 for each case of contravention - or in the alternative detention - or detention for up to six months, in case of repeated contravention for up to a total of two years, with said fine to be enforced against Defendant's managing directors, to refrain from

offering, placing on the market or using and from importing or possessing for the aforementioned purposes,

fulvestrant medicinal products, in particular Fulvestrant Hexal,

for the treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment,

within the territory of the Federal Republic of Germany,

by

offering, placing on the market or using or importing or possessing fulvestrant medicinal products, in particular Fulvestrant Hexal, for the aforementioned purposes in the Federal Republic of Germany, without precluding their use in the treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment in the Federal Republic of Germany,

in particular by

(a) having included in section 4.1 of the prescription information and in section 1, 2nd paragraph of the patient leaflet an exclusion of use in the event that the previous treatment with an aromatase inhibitor and tamoxifen failed;

(b) including in any and all advertising and information material relating to Fulvestrant Hexal, also including Defendant's website, an explicit, prominent warning that Fulvestrant Hexal may not be used to treat patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment;

(c) writing to the following addressees, with a copy to Plaintiff's attorney of record, (i) noting that Fulvestrant Hexal may not be used for the treatment of patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment; and (ii) asking them to inform their members accordingly that, in order to avoid patent infringements, for the patient population Faslodex® must be prescribed excluding aut-idem substitution:

- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) [German society for gyneacology and obstetrics],
- Deutsche Gesellschaft für Hämatologie und medizinische Onkologie (DGHO) [German society for hematology and medical oncology],
- Berufsverband Niedergelassener Gynäkologischer Onkologen (BNGO) [professional association of practice-based gynaecological oncologists],
- Berufsverband der Niedergelassenen Hämatologen und Onkologen (BNHO) [professional association of practice-based hematologists and oncologists],

- Arbeitsgemeinschaft Gynäkologische Onkologie Kommission Mamma (AGO) [association of gyneacological oncology commission mamma],
- Deutsche Krankenhausgesellschaft (DKG) [German hospital society],
- Bundesverband Deutscher Krankenhausapotheker (ADKA) [federal association of German hospital pharmacists],
- Deutscher Apothekerverband (DAV) [German association of pharmacists] / Bundesvereinigung Deutscher Apothekerverbände (ABDA) [federal association of German pharmacist associations], and
- Kassenärztliche Vereinigung [associations of statutory health insurance physicians]; and

(d) writing to the statutory health insurance funds, with a copy to Plaintiff's attorney of record, indicating that Fulvestrant Hexal may not be used to treat patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment;

2 in the alternative: under penalty of a fine to be imposed, but not exceeding EUR 250,000 for each case of contravention - or in the alternative detention - or detention for up to six months, in case of repeated contravention for up to a total of two years, with said fine to be enforced against Defendant's managing directors, to refrain from offering and/or supplying

fulvestrant medicinal products, in particular Fulvestrant Hexal,

for the treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment,

to buyers in the Federal Republic of Germany,

without

(a) having included in section 4.1 of the prescription information and in section 1, 2nd paragraph of the patient leaflet an exclusion of use in the event that the previous treatment with an aromatase inhibitor and tamoxifen failed;

(b) including in any and all advertising and information material relating to Fulvestrant Hexal, also including Defendant's website, an explicit, prominent warning that Fulvestrant Hexal may not be used to treat patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment;

(c) writing to the following addressees, with a copy to Plaintiff's attorney of record, (i) noting that Fulvestrant Hexal may not be used for the treatment of patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment; and (ii) asking them to inform their members accordingly that, in order to avoid patent infringements, for the patient population Faslodex® must be prescribed excluding aut-idem substitution:

- Deutsche Gesellschaft für Gynäkologie und Geburtshilfe (DGGG) [German society for gyneacology and obstetrics],
- Deutsche Gesellschaft für Hämatologie und medizinische Onkologie (DGHO) [German society for hematology and medical oncology],
- Berufsverband Niedergelassener Gynäkologischer Onkologen (BNGO) [professional association of practice-based gynaecological oncologists],
- Berufsverband der Niedergelassenen Hämatologen und Onkologen (BNHO) [professional association of practice-based hematologists and oncologists],
- Arbeitsgemeinschaft Gynäkologische Onkologie Kommission Mamma (AGO) [association of gyneacological oncology commission mamma],
- Deutsche Krankenhausgesellschaft (DKG) [German hospital society],
- Bundesverband Deutscher Krankenhausapotheker (ADKA) [federal association of German hospital pharmacists],
- Deutscher Apothekerverband (DAV) [German association of pharmacists] / Bundesvereinigung Deutscher Apothekerverbände (ABDA) [federal association of German pharmacist associations], and
- Kassenärztliche Vereinigung [associations of statutory health insurance physicians]; and

(d) writing to the statutory health insurance funds, with a copy to Plaintiff's attorney of record, indicating that Fulvestrant Hexal may not be used to treat patients who previously have been treated with an aromatase inhibitor and tamoxifen and have failed with such previous treatment;

3. furnishing Plaintiff without undue delay and in writing

a) with information about the extent to which it (Defendant) has performed the activities as per clause I.1 since 12 October 2005, indicating

aa) the names and addresses of the manufacturers, suppliers and other prior possessors,

ab) names and addresses of buyers as well as points of sale, for which the products were intended,

ac) the quantity of the produced, delivered, received, or ordered products as well as the price paid for the relevant products, and

b) rendering account as to the extent to which it has committed the acts specified in section I.1. since 12 November 2005, by submitting a separate schedule, in particular indicating:

aa) the individual deliveries, broken down by delivery quantities, times and prices, including product designations as well as the names and addresses of buyers;

ab) the individual offers, broken down by offer quantities, times and prices, including product designations as well as the names and

addresses of the offer recipients;

ac) the advertising performed, broken down by advertising media, their circulation figures, dissemination period and dissemination area, and

ad) prime costs itemized by individual cost factors and the profits generated,

whereby

the points of sale, purchase prices and selling prices are to be indicated only for the period from 30 April 2006, and

as evidence for said information, copies of the corresponding purchasing and sales documents (invoices or bills of delivery) shall be submitted, whereby confidential details other than the required data may be redacted;

II. to find that Defendant is obligated to compensate Plaintiff for any damages caused and still being caused by the actions pursuant to clause I.1, carried out subsequent to 12 November 2005.

It furthermore suggests fixing the security for enforcement separately for each judgment and allowing to avert enforcement by Defendant against security bond.

Defendant requests that

the appeal be dismissed,

1. in the alternative, in the event that motions 1. or 1 .(a) should have to be upheld,

it - Defendant - will be obligated to apply to the competent regulatory authority under Regulation (EC) No 1234/2008 for including the following addition to clause 4.1 of the prescription information in accordance with Exhibit HE 7 as well as in clause 1, 2nd paragraph of the patient leaflet in accordance with Exhibit HE 6:

"For patent reasons, Fulvestrant Hexal® must not be used for the palliative treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment."

2. in the alternative, in the event that motions 2. or 2.(a) should have to be upheld, it - Defendant - will be obligated to apply to the competent regulatory authority under Regulation (EC) No 1234/2008 for including the following addition to clause 4.1 of the prescription information in accordance with Exhibit HE 7 as well as in clause 1, 2nd paragraph of the patient leaflet in accordance with Exhibit HE 6:

"For patent reasons, Fulvestrant Hexal® must not be used for the palliative treatment of a patient with breast cancer who previously has been treated with an aromatase inhibitor and tamoxifen and has failed with such previous treatment."

in the further alternative,

with regard to Plaintiff's motions 1. and 1.(a) or 2. and 2.(a), it - Defendant - be granted transition period of no less than 300 days;

in the further alternative,

the proceedings be stayed pursuant to Sec. 148 ZPO (Civil Procedure Code) until the first-instance decision on the nullity complaint concerning patent EP 1 272 195 B1 has been reached;

in the further alternative,

it - Defendant - be allowed to avert enforcement against security bond (bank or savings bank guarantee).

Defendant defends the judgment under appeal as correct and furthermore maintains its legal defence submitted already in the first instance.

The complaint is said inadmissible already due to a breach of the obligation to consolidate claims (Sec. 145 PatG (Patent Act)), since - as is undisputed - an infringement complaint regarding the German part of Plaintiff's European patent 2 266 573, addressing the same challenged embodiment, has been pending between the Parties before the Regional Court Mannheim (2 O 256/15) since 14 December 2015. In said legal dispute, Plaintiff allegedly also had to introduce the patent in suit in the case at hand.

The demand for relief furthermore is said to also lack merit. It is deemed to fail already because the challenged embodiment is not evidently prepared for the patented use (breast cancer treatment after failed treatment with tamoxifen and an aromatase inhibitor). Even if the requirement of customizing were waived in certain circumstances, which is not legally justifiable, the challenged embodiment is said not to be suitable for the patented use, which is not least demonstrated by the fact that Plaintiff's original product Faslodex® is not approved for use pursuant to the invention. Allegedly there also is no prescription practice that leads to the use of fulvestrant pursuant to the invention. Because if the patent in suit is understood correctly, it would be possible to speak of a failure of the pre-treatment only if the administration of tamoxifen and an aromatase inhibitor was palliative - and not only adjuvant - in view of a manifest tumor. Based on this assumption, then according to Plaintiff's own figures from the special evaluation of iOMEDICO AG, the scope of use is not sufficient. This is especially the case, since those figures are not meaningful already due to the small database, but also because significant changes have occurred since the survey, in so far as a new class of active substances (CDK4/6 inhibitors) has been approved, which would also be promising in combination with fulvestrant.

Adding an exclusion of the patented use in the prescribing information and patient leaflet allegedly is legally impossible for it (Defendant); affixing a warning notice to advertising and information materials is deemed misleading under competition law against the background of the provisions of the HWG (Law on the Advertising of Medicines). There is no claim basis for Plaintiff's request to write to members and to the statutory health insurance funds.

Ultimately, in the context of the nullity proceedings, the patent in suit will also be found to be legally invalid.

Regarding the details of the facts of the case and the status of the dispute, reference is made to

the contents of the court files, together with exhibits.

II.

The admissible appeal is unsuccessful on the basis of its merits.

1.
The complaint is admissible. Sec. 145 PatG does not preclude its filing in separate proceedings.

In the judgment under appeal (reprint p. 10), the Regional Court substantiated in detail that and why Plaintiff was not required to introduce its claims under the patent in suit in the proceedings brought in December 2015 with the Regional Court Mannheim against the same challenged embodiment under EP 2 266 573. It has explained that the subject-matter of the two complaints does not constitute "the same action" within the meaning of Sec. 145 PatG, which is the case only if the infringing facts are identical in terms of the form as specified by the features of the demands for relief (Benkard/Grabinski/Zülch, PatG, 11th ed. § 145, margin no. 6), which is deemed not to be the case here, as a formulation patent is at issue before the Regional Court Mannheim, whereas in the present case concerns a provisional use patent. A "similar act", which allegedly has to be assumed if, due to the close technical relationship, it is downright necessary to challenge certain infringing acts together in one single complaint under several patents in order to spare Defendant having to litigate several complaints (BGH (Federal Court of Justice) GRUR 2011,411- Raffvorhang; Benkard/Grabinski/Zülch, PatG, 11th ed. § 145 margin no. 6), allegedly also cannot be assumed. In the present complaint, completely different issues arose with regard to the completely different subject matter of the patent than was the case in the legal dispute before the Regional Court Mannheim.

Those considerations do not indicate a legal error; Defendant does not even begin to demonstrate such an error.

2.
However, the complaint is unjustified. Ultimately, the Regional Court has rightly denied an infringement of the patent in suit by the challenged embodiment and accordingly dismissed the complaint.

1.
The patent in suit relates to the treatment of breast cancer.

a)
According to the explanations in the specification of the patent in suit, estrogens (which until menopause are formed in the ovaries, but - regardless of menopause - in other tissues as well) act as growth factors for at least one-third of breast cancers (para. [0004]). It thus is a recognized treatment approach in breast cancer therapy to withdraw estrogen in the patient, which in premenopausal women is achieved by the (surgical, radiotherapeutic, or medical) removal/deactivation of the ovaries, preventing the production of new estrogen, while in postmenopausal women the conversion of other hormones into estrogen is blocked by aromatase inhibitors (para. [0005]).

According to the patent in suit, a known alternative to the described estrogen withdrawal is to use antiestrogens - primarily tamoxifen. Their function is to bind to and compete for estrogen receptors present in hormone-responsive tumor cells, thus blocking the estrogen from binding to

the tumor (para. [0006]). One disadvantage of tamoxifen, however, is its partially agonistic effect, which results in an incomplete blockade of estrogen-mediated activity (para. [0006]).

Accordingly, it was already common in therapeutic practice to treat postmenopausal women with advanced breast cancer whose disease has progressed following treatment with tamoxifen, with an aromatase inhibitor (such as anastrozole or letrozole) (para. [0007]; note: In premenopausal patients, the administration of an aromatase inhibitor is out of the question because it would not prevent the estrogen production in the ovaries from still functioning).

Against said background, the object of the invention must be considered as indicating a therapy for the (so far unmanageable) case that - following unsuccessful treatment with tamoxifen - the subsequent treatment with an aromatase inhibitor fails as well (para. [0007] at the end; Technical Board of Appeal 3.3.02, decision of 14 February 2013, Exhibit HE 4a, p. 11 margin no. 2.4.3).

To solve this problem, the patent in suit suggests continuing the breast cancer treatment - which was unsuccessful when treated with tamoxifen and an aromatase inhibitor in sequence (para. [0007] sentence 1) - with fulvestrant. In detail, patent claim 1 protects the following combination of features:

1. Use of fulvestrant in the preparation of a medicament.

2. The medicament is used for the treatment of a patient with breast cancer.

3. Who previously has been treated

   a) with an aromatase inhibitor

      and

   b) with tamoxifen

   and has failed with such previous treatment.

b)
According to the invention, it remains to be seen whether tamoxifen was used first, followed by an aromatase inhibitor, or whether the approach was reversed. However, the necessary condition for any use of the patent is that the two active substances are administered sequentially one after the other - and not simultaneously; even Plaintiff does not claim otherwise.

It is also of significance to note that the successive treatment with both active substances has failed, i.e. neither tamoxifen nor the aromatase inhibitor led to any therapeutic success. Hence, the mere use of fulvestrant following prior treatment with tamoxifen and an aromatase inhibitor as such does not satisfy the requirements of the patent claim, but only a therapeutic use of fulvestrant, which is caused by a failure of the other, primarily performed treatment approaches (tamoxifen and aromatase inhibitor). Because the patent claim is not satisfied with fulvestrant being used as a third therapeutic agent at all, but also explicitly refers to the fact that the previous treatments with tamoxifen and an aromatase inhibitor have failed, i.e. (as will be discussed again later) *each one of them* has failed and treatment with fulvestrant *therefore* is started and continued.

c)
The failed treatment with tamoxifen and an aromatase inhibitor, which the fulvestrant patient must have undergone previously, must be a palliative breast cancer therapy - and not only an adjuvant one. The Regional Court's different understanding that even an adjuvant drug administration of tamoxifen and an aromatase inhibitor following cancer surgery, i.e. one that with regard to cancer cells not removed with the intervention is purely preventive, is sufficient if new cancer is subsequently detected, does not do justice to the content of the patent specification that is relevant for the interpretation.

aa)
A mere adjuvant administration of tamoxifen and an aromatase inhibitor, as it is customary following the surgical removal of a breast cancer tumor, indeed can also be understood in the literal sense of the word as a "treatment" within the context of cancer therapy. Because this is done according to medical-therapeutic rules for the purpose of eliminating *any* undetected cancer cells with medication that subsequently *might* spread.

bb)
However, with regard to a merely adjuvant treatment - as Defendant rightly claims - it frequently is in fact impossible to judge at all whether it has "failed", with the consequence that it cannot be regarded as "previous treatment", where unsuccessful implementation necessarily is required by claim 1 of the patent in suit.

(1)
This already is clearly shown by the scenario commonly used in practice, i.e. that the breast cancer tumor was surgically removed and then tamoxifen was administered prophylactic (adjuvant) first for a predetermined period (e.g. two years) and then an aromatase inhibitor was administered as part of a switch therapy for a further predetermined period (e.g. three years) in order to prevent the possible risk of the cancer spreading. If this occurs in such a constellation after completion of the switch treatment (e.g. in the sixth year after surgery), it is not possible to make a reliable statement to the effect that *both* pre-treatments, and hence also the first treatment with tamoxifen, have failed to be effective; instead, the return of the disease after completion of the treatment cycle may also (and possibly even more likely) be caused by the fact that the switch to an aromatase inhibitor has cleared the path for tumor formation that had previously been successfully blocked by treatment with tamoxifen. The situation is similarly imponderable if repeated tumor formation has occurred during therapy with an aromatase inhibitor, albeit after a considerable lag after completion of the treatment with tamoxifen; here, too, the causal connection can easily be such that the relapse can be attributed to the change in treatment to the aromatase inhibitor, which - in contrast to tamoxifen - is not effective. On the other hand, whether a particular cancer therapy (namely treatment both with tamoxifen as well as the subsequent or preceding treatment with an aromatase inhibitor) has failed can be assessed clearly and conclusively if the treatment is palliative with a tumor that has manifested over the course of the therapy. The therapy results, which without doubt have been shown with treatment with tamoxifen and an aromatase inhibitor, provide clear evidence as to whether or not the growth of the tumor has progressed compared to the state prior to the respective start of the treatment. This consideration already indicates that only palliative treatment results should be considered in the context of the patent in suit.

(2)
A confirmation of this view can be found in various places of the patent description. Reference

should first be made to paragraph [0018], which for the patent in suit defines in legal terms, how the term "failed" used by the patent in suit in connection with the pre-treatments should be interpreted. It states there:

> *By the use of the term "failed" we mean that* ***growth of the breast cancer is no longer arrested*** *by treatment with an aromatase inhibitor or tamoxifen, or both an aromatase inhibitor and tamoxifen together.*" (note: emphasis added)

Since only tumor cells can "*grow*" and since only the growth of tumor cells *"can be arrested"*, the person skilled in the art understands that the term *"the breast cancer"* refers to the mamma carcinoma (where growth cannot be arrested when treated with tamoxifen and an aromatase inhibitor) in the same way as the German translation of the patent description. In a technically expedient understanding, even the definition of the patent in suit itself thus states that a failure of the pre-treatment can be determined on a manifest tumor that has been treated palliatively with tamoxifen and an aromatase inhibitor.

(3)
Thus, all further advantages set forth of the patent specification (note: emphases added for clarification) are also identical. For example, para. [0009] emphasizes that fulvestrant has already demonstrated efficacy in a phase-II trial in women whose breast cancer has progressed following tamoxifen therapy and para. [0011] emphasizes that fulvestrant has a marked inhibitory effect on the growth of MCF-7 breast cancer cells in humans and has shown a significantly higher reduction in MCF-7 cell counts compared to tamoxifen. Paragraph [0012] refers to studies showing that tamoxifen-resistant MCF-7 tumors, which grow out after long-term treatment with tamoxifen, remain sensitive to fulvestrant treatment and that fulvestrant suppressed the growth of established MCF-7 tumors for twice as long as treatment with tamoxifen. Finally, para. [0013] describes the finding as surprising that following previously failed treatment *with both* an aromatase inhibitor *as well with* tamoxifen, breast cancer is *sensitive* to further treatment with fulvestrant. The above-cited passage of the description is of particular importance, since the patent description, referring to a finding that is surprising for the person skilled in the art, emphasizes the actual idea of the invention, i.e. that in spite of the double resistance to both tamoxifen and an aromatase inhibitor associated with the cumulatively failed pre-treatments, the efficacy (sensitivity) of the cancer to fulvestrant remains. All of the above-cited remarks are based on a common notion of the efficacy of fulvestrant in palliative control (further treatment) of a manifest tumor.

(4)
It is not least completely consistent with the explanations made in para. [0007] of the patent specification regarding prior art and - based thereupon - the progress to be made by the invention. According to the above statements it was known that postmenopausal women with breast cancer, where the disease progressed after treatment with tamoxifen, were given an aromatase inhibitor such as anastrozole or letrozole to achieve therapeutic success. The subsequent second-line therapy with anastrozole or lestrozole following the cancer not arrested by way of treatment with tamoxifen thus represents palliative treatment of a manifest (progressive) tumor. As mentioned above, given this starting situation, the patent in suit is focused to the object of providing a treatment approach in the event that second-line treatment with an aromatase inhibitor (anastrozole or lestrozole) also fails. In this respect, reference is made to the situation known in prior art, i.e. treating a breast cancer tumor which progresses in spite of tamoxifen treatment which cannot be arrested even with the effect of an aromatase

inhibitor. The solution of the patent in suit, i.e. to administer fulvestrant as third active substance in the event of failure of second-line treatment with an aromatase inhibitor recommended by prior art, thus also refers to the tumor - which manifests in spite of two pre-treatments.

(5)
The Board of Appeal's decision of 14 February 2013 is not based on any other understanding of the invention. On the contrary, even there, the contribution of the patent in suit is considered throughout as recommending fulvestrant for third-line treatment of doubly resistant breast cancer (cf. margin no. 2.4.4, 2.4.5, in the middle) and in the context of examining the inventive step, the stronger resistance to therapy resulting of each tumor treatment is used as an argument. Margin no. 2.4.6 states in this regard - in excerpts - as follows (note: emphases added):

> *"When assessing whether the use of fulvestrant as a third-line agent ... is obvious, the following factors must be considered:*
>
> *(a) With each new resistance, the* tumor becomes "more malignant" and harder to treat*. Consequently, it is by no means a given that an active substance that is effective in second-line treatment, is suitable for* third-line treatment*.*
>
> *(b) If the* tumor -... - is resistant to an aromatase inhibitor *and a partial estrogen agonist such as* tamoxifen, *the person skilled in the art would tend to choose a* third-line agent *whose mechanism of action is different from that of a partial estrogen agonist and an aromatase inhibitor. However, whether this would cause the person skilled in the art to consider a compound such as fulvestrant is questionable in light of the fact that fulvestrant … is not fundamentally different from tamoxifen in terms of its mechanism of action. … Under these circumstances, a compound like fulvestrant thus would not have been the first choice for the person skilled in the art."*

(6)
On the other hand, the specification of the patent in suit does not provide any indication that a mere adjuvant pre-treatment might be relevant. The protocol outlined in para. [0028] et seq., which in the patent specification (para. [0028]) is identified as the preferred embodiment of the invention, indeed provides for even considering patients who received the active substance tamoxifen before being treated with anastrozole or letrozole (para. [0038]). However, it follows from para. [0037] that the disease must have progressed during treatment with anastrozole or letrozole, which means that treatment with the aromatase inhibitor was palliative. Nothing else applies to the earlier tamoxifen therapy, which according to the text of the description cannot have taken place "either" as additional therapy (adjuvant) "or" for the treatment of an advanced cancer (palliative), but which must have been "both" additional "as well as" palliative. However, ultimately, this can even be due to the fact that the protocol is in any case beyond the current version of the claim of the patent in suit, since it is based on the situation - which is not in accordance with the patent - of only a single failure of a pre-treatment (sic.: with an aromatase inhibitor).

(7)
Precisely due to the fact that a single failure is not sufficient, the patent claim was limited in the course of the grant procedure such that patent protection is not granted already - as originally applied for - for the use of fulvestrant after unsuccessful cancer treatment with an aromatase

inhibitor (single resistance), but only applies if a pre-treatment with tamoxifen - and hence a double resistance of the cancer to be treated - has also turned out to have failed. For the purposes of the invention, para. [0018] indeed legally defines the term "failure" as *growth of the breast cancer is no longer arrested by treatment with an aromatase inhibitor, or tamoxifen, or both*", whereby at first glance, it might be concluded from the word "or" that, in the context of the invention, the finding of a concrete failure is sufficient only in respect of one active substance, i.e. either the aromatase inhibitor or tamoxifen. However, such an understanding would be in stark contrast to the entire remaining content of the patent specification as explained above, and hence cannot be a meaningful interpretation for the average person skilled in the art. Instead, he will understand said passage of the description as an explanation that is owed to the original, significantly more extensive application content and which - just like the clinical trial plan pursuant to example 1 - lies outside the applicable notion of the invention and which therefore correctly should have been partially deleted during the grant procedure (namely with regard to a failure of only one pre-treatment).

2.
Based on the above-mentioned understanding of the patent in suit and its technical teaching, a patent infringement can be ruled out in case of dispute.

a)
As Plaintiff concedes, the product at issue has not been evidently prepared by Defendant for use pursuant to the patent. Insofar as the patient leaflet addresses palliative pre-treatment at all, it refers to a progression of cancer under treatment with an antiestrogen. In contrast, the further failed pre-therapy with an aromatase inhibitor, as required by the patent in suit, is not mentioned at all. The same applies - which should be noted here only as a precaution - if an adjuvant pre-therapy is taken into consideration, since the patient leaflet also does not mention the failed adjuvant use of an aromatase inhibitor.

b)
However, according to the Senate's case law (GRUR 2017, 1107 - Östrogenblocker) - since the objective suitability of the relevant drug for the patented use is at the center of the protection conferred by a provisional use patent (BGH, GRUR 2016, 921 - Pemetrexed) - in exceptional cases, a liability of the distributor of the product is conceivable even without measures of evident customizing of its own.

aa)
Considering the not all-encompassing, but limited substance protection, i.e. for a specific substance protection, only prerequisites must be met: Firstly, the product must be suitable for the patented purpose and secondly, the distributor must utilize circumstances, which similar to evident configuration ensure that the evident customizing is used for the specific therapeutic purpose. The latter requires an adequate and not only isolated scope of use in accordance with the patent in suit as well as relevant knowledge by the vendor or at least unconscionable failure to take note of the relevant information on the part of the vendor (Senate, GRUR 2017, 1107 - Östrogenblocker). If the generic drug maker is or at least should have been familiar with the prescription practice which is favorable for it and if it nonetheless exploits this proactively by supplying its wholesalers, it is adequate to hold the generic drug maker liable under patent law for this.

(1)

The Senate has not yet decided to what extent the use without customizing must take place in accordance with the provisions of the patent in suit in order to establish liability. The following considerations, which are oriented to the customizing situation, are decisive: The evident customizing does not have to specify the patented use as the sole and exclusive purpose of use; instead, all that is important is that the use pursuant to the invention - possibly in addition to others - is indeed part of the use instigated by the customizing. Accordingly, both the constellation where the patient leaflet itself mentions several possible uses, including the patented use is relevant, as well as the case where the patient leaflet only relates to the protected use, but it is obvious that there are other, competing areas of use. Since this is a fact, even in cases of cross-label-use, which does not require customizing, not only such use which concerns exclusively or almost exclusively the patented use may be relevant for liability. Instead, the certain knowledge (which is equal to ignoring facts) is crucial that the marketed medicine will actually lead to the patented application and use. For with regard to the consequences, a person acting with said knowledge must be treated so as if he/she him-/herself had brought about the condition without customizing he/she has commercially exploited through a corresponding customizing measure. This means that a trial judge must - first - established that there has been sufficient patented use and that - secondly - the generic drug company simply cannot have been unaware of this fact. With the number of demonstrable cases of patented use, the chance of such a finding made by a trial judge naturally increases; accordingly, the isolated cases that have occurred generally cannot give rise to liability without customizing. A further liability scenario may follow from particular, outstanding advantages of the patented use compared to other therapeutic purposes, which indeed ask for using the product in accordance with the patent - and not in any other way.

(2)
If - as in the present case - a prescription drug is concerned, which can be expected to be taken only in accordance with the medical prescription in terms of application and dosage, the prescription practice is decisive, which has to be taken into account based on the content of the means to be made available to the physician for his/her prescription. Insofar, the prescribing information, which is an integral part of the drug approval and conclusively defines the features of its version approved for distribution, is of central importance. Because the approved version of the medicinal product *must* be identical with the marketed version, life experience has shown that the physician will prescribe the individual drugs only in accordance with their respective specific prescribing information, with the effect that a generic drug which - unlike the originator's product - does not have a specific (patented) indication/dose, e.g. for reasons under patent law, will in fact not be prescribed to a patient for this purpose, and this is why the generic drug also will - subsequently - not be used therapeutically in this sense.

(3)
Nevertheless, it makes quite a significant difference to the liability for injunctive relief whether the medicinal product was evidently customized or not: If the liability of the generic drug company (or other distributor) is based on evident customizing of the product for the patented use, then every individual case of infringement (= evident customizing with subsequent offer/sale), including the very first and only one, is based on general rules, the risk of future repetition (of the distribution of evidently customized products and their subsequent use in accordance with the customizing); this readily leads to an injunction order, unless the infringer submits - under penalty of law - a declaration of submission prior to going to court. The situation is completely different in the case of a distributor who has not undertaken any customizing measure and whose liability should be solely based on an actual prescription practice corresponding to the protected use. Even if

sufficient actual use has been made in the past (which leads to the distributor's obligation to pay damages and provide information for the period in question), an injunction order can only be considered if a prescription exercise relevant to liability can still be established at the present time, i.e. at the time of the hearing. If this is not the case, because the product previously had been used cross-label, but prescription practice has changed since (e.g. because of new active substances that have increasingly replaced the medicinal product in question as a therapeutic), an injunction order has to be ruled out. For - unlike liability for evident customizing product - it is not linked to a certain conduct on the part of the infringer, which according to life experience, can be expected to be repeated, giving rise to causality, but is solely based on certain external framework conditions (sic: actual handling of prescriptions), which, if they no longer apply over time, also can no longer form the basis for any cease-and-desist obligation on the part of the distributor.

bb)
Plaintiff's arguments do not indicate that, based on the basis of actual prescription practice, Defendant's product at issue is, or has been, used to a sufficient extent in cases where the cancer patient has previously been treated with both tamoxifen and an aromatase inhibitor without palliative success.

(1)
According to the special evaluation by iOMEDICO AG - which can be assumed to be accurate in favor of Plaintiff and where even Plaintiff insists that its results are representative - the following data must be assumed for the use of fulvestrant following palliative pre-treatment with tamoxifen and an aromatase inhibitor:

Period of treatment with fulvestrant:	2007-2009	2010-2012	2013-2014	2015-2016
… % of breast cancer patients:	6.9	3.1	2.2	0.0

This means that at most, less than 7% of all cancer patients treated with fulvestrant had without success undergone palliative pre-treatment with tamoxifen and an aromatase inhibitor. Already in view of this clearly single-digit numerical value, the prescription practice leading to the use of the invention occurs only occasionally and by no means to such an extent that Defendant could not have overlooked under any circumstances. Plaintiff, which justifies its claims by invoking the overall palliative and adjuvant use of fulvestrant, which averaged 45.7% over the years, does not specifically show that and why Defendant could not have overlooked a (solely relevant) palliative scope of use of less than 7%, which is in a completely different order of magnitude. All demands for relief have to be ruled out for this reason alone. With regard to the future-oriented claim for injunctive relief, any liability on the part of Defendant is especially out of the question, since - as of the date of the hearing (09 January 2019) - not a single case of a fulvestrant prescription pursuant to the patent, i.e. following unsuccessful palliative pre-treatment with tamoxifen and an aromatase inhibitor can be demonstrated for the last four years. Accordingly, it is simply not possible to ascertain a regulatory practice leading to a patent-protected use for the relevant current point in time. Since initiation of the proceedings, Defendant may indeed have been aware of the prescription practice corresponding to the patent due to the evaluation presented to it; from that time onward, this might support the allegation that Defendant had deliberately utilized the practice of off-label use by supplying customers without any change, thus giving rise to liability;

however, Plaintiff's data, which already show a value of nil for the years 2015 and 2016, i.e. long before pendency, do not show that such supply made by Defendant with knowledge of the facts of the case led at least once to a prescription and use pursuant to the patent.

(2)
The affidavit of Plaintiff's privately retained expert, Prof. Dr. Jackisch dated 14 February 2017 (Exhibit HE 9) does not lead to any other findings compared to the data from the special evaluation in favor of Plaintiff. Insofar as insurance - in any case based on only subjective estimations of the author - specifies figures of a treatment with fulvestrant, they concern without exception patients, who previously had undergone *adjuvant* treatment with tamoxifen and an aromatase inhibitor, without any closer breakdown being made in this respect. Prof. Dr. Jackisch does not comment on the issue, in how many cases fulvestrant was administered after a failed palliative pre-treatment with the aforementioned active substances.

cc)
Moreover, the result of lack of patent infringement would be no different if such adjuvant pre-treatments were taken into account which have been shown to be ineffective in the treatment of the breast cancer suffered by the patient to be treated. The data presented by Plaintiff do not permit specific findings to be made in that regard.

The special evaluation in fact provides for a separate case group of patients who have undergone adjuvant (i.e. post-surgical prophylactical) treatment with one active substance (tamoxifen or an aromatase inhibitor) and palliative treatment with the respective other active substance (i.e. an aromatase inhibitor or tamoxifen); this indicates that a new cancer tumor must have occurred prior to palliative treatment, as otherwise there would be no reason for palliative therapy. The adjuvant pre-treatment could be considered as "failed" if the tumor reappeared during the ongoing adjuvant pre-treatment or in close temporal relation to its termination. In that case it would be clear that the first (adjuvant) pre-treatment would have failed, since another tumor had appeared during such treatment. If fulvestrant has been administered immediately after palliative pre-treatment, it would also have to be assumed that the second palliative therapy failed, as its failure was the reason for fulvestrant-therapy.

However, the special evaluation does not make it possible to determine without any doubt whether the conditions were actually like this or whether (and if so to what extent) the tumor during the palliative second-line treatment was initially arrested - which would rule out the assumption of a failure - and fulvestrant (e.g. for reasons of a possible interim intolerance or contraindication) was administered only some time later, as a tumor occurred again some time after the successful palliative treatment, during and as a result of the interval without any treatment. The deliberations at the hearing on 09 January 2019 also did not provide any clarity in this regard.

Notwithstanding the foregoing, an injunction order is out of the question in particular, since - including the additional case group ("one adjuvant, one palliative") - according to the special evaluation, a total patent-appropriate scope of use of only 1.9 % can be assumed for the period from 2015 to 2016. This value as such is already completely inadequate for any liability on the part of Defendant; this is especially the case when considering that for the preceding period from 2013 to 2014 even significantly higher values are shown ("one adjuvant, one palliative": 15.7 %; "both palliative": 2.2 %) and that it is furthermore taken into account that the values for 2015 to 2016 - which are marginal already - are based on a significantly lower number of patients (of 52)

than the figures of the previous years (174, 129, 89). The outlined course allows for only a single forecast for 2017 and 2018, namely that of a further significant decrease of 1.9% of the scope of use pursuant to the patent; this means that in view of the current irrelevance of the palliative as well as the partly adjuvant and partly palliative use of fulvestrant, a claim for injunctive relief must be excluded.

III.

The judgment on the costs follows from Sec. 97 para. 1 ZPO.

The provisional enforceability orders are based on Sec. 708 no. 10, 711 ZPO.

There is no reason to admit the revision because the conditions laid down in Sec. 543 ZPO obviously are not met. As a purely individual decision on patent interpretation, the case has neither fundamental significance within the meaning of Sec. 543 (2) no. 1 ZPO nor does the safeguarding of uniform case law or the further development of the law require a decision by an appellate court within the meaning of Sec. 543 (2) no. 2 ZPO. The same applies with regard to the legal question not yet decided by the Federal Supreme Court, i.e. whether the liability of a generic drug company may also be considered independently of a meaningful production of its product.

In view of the data situation presented by Plaintiff, the scope of use pursuant to the patent is so small that - even if one wanted to assess the fundamental legal question (as the Senate does) in favor of the property right holder - any liability on the part of Defendant is not conceivable under any circumstances.

Dr. Kühnen Fricke R. Thomas