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DISTRICT COURT OF THE HAGUE

Team Trade - preliminary relief judge

Case number / role number: C/09/653142 / KG ZA 23-730

Summary judgment of 3 October 2023

in the case of

1. the legal person under foreign law
GRÜNENTHAL GMBH,
Aachen, Germany,
2. GRÜNENTHAL B.V.,
in Bunnik, plaintiffs,
advocaat: mr. R.M. Kleemans in Amsterdam,

against

1. **TEVA B.V.**,
2. **TEVA NETHERLANDS B.V.,**
3. **PHARMACHEMIE B.V.,**
all of Haarlem,
defendants,
Advocate: Mr A.A.A.C.M. van Oorschot, Amsterdam.

Plaintiffs will hereinafter be referred to collectively as Grünenthal (female singular) and separately as Grünenthal GmbH and Grünenthal B.V. Defendants will hereinafter be referred to collectively as Teva et al (female singular) and separately as Teva B.V., Teva Nederland and Pharmachemie.

The case was substantively heard for Grünenthal by Mr Kleemans aforementioned, Mr A.H. van Duijn, lawyer in Amsterdam, and Dr M. Klok, patent attorney, and for Teva et al. by the aforementioned Mr Van Oorschot, Messrs O.P. Swens, S. Moonen and M. Hendriks, lawyers in Amsterdam, and Dr J.J.M. Verbart, patent attorney.

1. The procedure

1.1. The conduct of the proceedings is evidenced by:
- the interlocutory judgement of 13 September 2023 in which the interim injunction court ruled on the incidental claims pursuant to Section 223 Rv[1] (hereinafter: the interlocutory judgement) and ordered Teva c.s. to remove Testosterone Teva (or have it removed) from the October 2023 G-Standard with immediate effect and in any case before 17:00 on 13 September 2023, on pain of forfeiture of a penalty payment;

[1] Code of Civil Procedure

- Grünenthal's e-mail of 12 September 2023 to the court (sent with Teva c.s.'s consent).attaching the deed of partial surrender pursuant to article 63 ROW[2] which Grünenthal sent on 12 September 2023 (after the oral proceedings) to Octrooicentrum Nederland (hereinafter: OCNL), requesting that the attached limited claims be entered in the patent register as a matter of urgency.

2. The facts

2.1. Grünenthal is part of the Grünenthal Group, a German pharmaceutical company engaged in the development and production of pharmaceuticals, including a drug marketed under the brand name Nebido. Nebido was developed by Bayer AG and its production and sale was acquired by Grünenthal GmbH in 2022. Grünenthal B.V. holds the Dutch marketing authorisation for Nebido.

2.2. Nebido is a medicine with testosterone decanoate as active substance and is used to treat long-term testosterone deficiency in men (hypogonadism). It is administered (after a start-up phase) once every 10 to 14 weeks by intramuscular injection (hereafter: IM). The active substance, testosteroneundecanoate (hereinafter: TU), is a testosterone ester. This chemical compound is converted in the body into testosterone and a by-product. According to the Summary of Product Characteristics (hereinafter SmPC), Nebido is presented in an ampoule/injection vial containing 4 ml of solution containing 1000 mg TU (250 mg/ml) dissolved in a carrier of *castor oil* and the co-solvent benzyl benzoate (hereinafter BzBzo). The medicine contains 2000 mg of BzBzo in total, i.e. 500 mg/ml.

2.3. European patent EP 1 457 208 B9 (hereinafter EP 208 or the patent, the B1 text of which (was improved a short time after grant) for "*Methods and pharmaceutical compositions for reliable achievement of acceptable serum testosterone levels*" was granted to (a legal predecessor of) Bayer AG on 16 August 2006 for, inter alia, the Netherlands on an application of 15 March 2004, invoking priority of the Danish application DK 200300399 of 14 March 2003. Bayer AG transferred the patent in July 2022 to Grünenthal GmbH, which has been registered in the OCNL register as the holder of the Dutch part of EP 208 since 10 February 2023. The patent expires on 14 March 2024.

2.4. EP 208 (as granted) comprises 17 conclusions: conclusions 1 and 7 are independent formulation conclusions and conclusions 9 and 12 are independent use conclusions, repeating the composition of conclusion 1. Conclusions 2 to 6, 8 and 10, 11 and 13 to 17 are dependent conclusions. In the original English language, the conclusions read as follows:

1. A composition formulated for intramuscular injection comprising a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates; and a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.

[2] State Patent Act

2. The composition according to claim 1, wherein the testosterone ester is testosterone undecanoate.
3. The composition according to claim 2, wherein the testosterone undecanoate is in a dose of 150 to 500 mg per ml.
4. The composition according to any of the preceding claims, wherein the vehicle comprises the castor oil in a concentration of 25-40 vol%.
5. The composition according to any of claims 1-3, wherein the co-solvent is in an amount ranging from 55 to 65 vol% of the vehicle.
6. The composition according to any one of the preceding claims, wherein the co-solvent is benzyl benzoate.
7. A pharmaceutical formulation containing J,000 mg testosterone undecanoate in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume.
8. Use of a composition as defined in any one of claims 1-6 or a pharmaceutical formulation as defined in claim 7 in male contraception.
9. Use of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating primary and secondary hypogonadism in a man, said medicament is in a form for intramuscular injection and comprises a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.
10. The use according to claim 9, wherein said primary hypogonadism is derived from testicular failure selected from the group consisting of cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy and toxic damage from alcohol or heavy metals.
11. The use according to claim 9, wherein said secondary hypogonadism is derived from idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury caused by tumours, trauma or radiation.
12. Use of a of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicament for treating diseases and symptoms associated with deficient levels of testosterone in a man who is in therapy with a progestin or a gonadotropin suppressive agent, said medicament is in a form for intramuscular injection and comprises a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent.
13. The use according to claim 10, wherein said deficient levels of testosterone in a man is such that the concentration of testosterone in serum is less than 10 nmol/l.
14. The use according to claims 8-13, wherein the testosterone ester is testosterone undecanoate.
15. The use according to any of claims 8 to 14, wherein said medicament comprises said testosterone ester in a 6-week dose of 500 mg to 2000 mg, a 9-week dose of 500 mg to 2000 mg, a 10-week dose of 500 mg to 2000 mg, an 11-week dose of 500 mg to 2000 mg, a 12-week dose of 500 mg to 2000 mg, a 13-week dose of 500 mg to 2000 mg, a 14-week dose of 500 to 2000 mg, a 15-week dose of 500 to 2000 mg or a 16-week dose of 500 mg to 2000 mg.
16. The use according to claim 15, wherein said 6-, 9-, 10-, 11-, 12-, 13-, 14-, 15- and 16-week dose is of 750 mg to 1500 mg.
17. The use according to any of claims 8 to 16, wherein the co-solvent is benzyl benzoate.

2.5. The uncontested Dutch translation of these conclusions reads:

1. Compound formulated for intramuscular injection, comprising a testosterone ester chosen from the group of esters consisting of unbranched and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates; and a carrier comprising castor oil at a concentration of 25-45% by volume and a co-solvent.

2. Composition according to claim 1, wherein the testosterone ester is testosterone dodecanoate.
3. Composition according to claim 2, wherein the dose of testosterone dodecanoate is 150 to 500 mg per ml.
4. Composition according to any of the preceding claims, wherein the carrier contains castor oil at a concentration of 25-40% by volume.
5. Composition according to any of claims 1-3, wherein the amount of co-solvent varies between 55 and 65 per cent by volume of the carrier.
6. Composition according to any of the preceding claims, wherein the co-solvent is benzyl benzoate.
7. A pharmaceutical formulation containing 1000 mg testosterone decanoate in a 4-ml carrier of a mixture of castor oil and benzyl benzoate in a volume ratio of 1:1.7.
8. Use of a compound described in any of claims 1-6 or a pharmaceutical formulation described in claim 7 in male contraception.
9. Use of a testosterone ester selected from the group of esters consisting of unbranched and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a medicine for the treatment of primary and secondary hypogonadism in a man, wherein the medicine is in a form for intramuscular injection and includes a carrier, which includes castor oil at a concentration of 25- 45% by volume and a co-solvent.
10. Use according to claim 9, wherein the hypogonadism arose from testicular failure chosen from the group consisting of cryptorchidism, bilateral testicular torsion, testicular inflammation, orchiectomy, Klinefelter's syndrome, chemotherapy or toxic injury from alcohol or heavy metals,
11. Use according to claim 9, wherein the hypogonadism arose from idiopathic deficiency of gonadotropin-stimulating hormone (GnRH) or injury to the pituitary gland due to tumours, injury or radiation.
12. Use of a testosterone ester chosen from the group of esters comprise unbranched and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates for the preparation of a drug for the treatment of diseases and symptoms associated with reduced testosterone levels in a man under treatment with a progestativum or a gonadotropin-suppressing agent wherein the drug is in a form for intramuscular injection and comprises a carrier comprising castor oil at a concentration of 25-45% by volume and a co-solvent.
13. Use according to claim 10, where the reduced testosterone level in a man is such that the serum testosterone level is lower than 10 nmo1/1.
14. Use according to one of conclusions 8-13, where the testosterone ester is testosterundecanoate.
15. Use according to any of claims 8-14, wherein the drug includes the testosterone ester in a 6-week dose of 500 to 2000 mg, a 9-week dose of 500 to 2000 mg, a 10-week dose of 500 to 2000 mg, an 11-week dose of 500 to 2000 mg, a 12-week dose of 500 to 2000 mg, a 13-week dose of 500 to 2000 mg, a 14-week dose of 500 to 2000 mg, a 15-week dose of 500 to 2000 mg or a 16-week dose of 500 to 2000 mg.
16. Use according to claim 15, where the 6-, 9-, 10-, 11-, 12-, 13-, 14-, 15- and 16-weekly doses are 750 to 1,500 mg.
17. Use according to any of claims 8-16, wherein the co-solvent is benzyl benzoate.

2.6. The description of EP 208 includes - as far as relevant here - the following:

FIELD OF INVENTION

[0001] The present invention relates to the field of pharmaceutical formulation science as well as the field of therapeutic applications of hormones in hormone replacement therapy in men and in male

contraception. In particular, the invention relates to compositions of testosterone esters in castor oil that upon intramuscular injection provides reliable physiologically acceptable serum testosterone levels for a prolonged period.

BACKGROUND

(...)

[0003] Male hypogonadism is characterised by a deficiency of endogenous testosterone production resulting in abnormally low levels of circulating testosterone, i.e. serum testosterone levels below 10 nmol/l.

(...)

[0005] The clinical picture of hypogonadal adult men varies a lot. For example, testosterone deficiency is accompanied by symptoms of different severity, including sexual dysfunction, reduced muscle mass and muscle strength, depressed mood and osteoporosis.

[0006] Current standard therapies aims at restoring physiologically relevant levels of testosterone in serum, which applies to concentrations of about 12 nmol to about 36 nmol. Intramuscular injection of testosterone esters, such as testosterone enanthate or testosterone cypionate, administered every two to three weeks, still represents the standard of testosterone replacement therapy in most countries of the world. Apart from the inconvenience of frequent visits to the doctor's office, the patients complain about variations in well-being due to short-term fluctuations of serum testosterone levels resulting from the pharmacokinetic profile after intramuscular injection of for example testosterone enanthate.

[0007] Recently, the use of testosterone esters with longer aliphatic chain length and/or higher hydrophobicity, such as testosterone undecanoate, has become interesting in terms of prolonging the interval between injections. Longer intervals between injections are advantageous from a patient's point of view.

[0008] For example Zhang G et al, 1998, report the injection of compositions comprising testosterone undecanoate in a concentration of 250 mg in 2 ml of tea seed oil so as to administer a dose of 500 mg or 1000 mg of testosterone undecanoate (*Zhang G et al, A pharmacokinetic study of injectable testosterone undecanoate in hypogonadal men. J. Andrology, vol 19, No 6, 1998*). Zhang et al, 1999, relates to injectable testosterone undecanoate as a potential male contraceptive (*Zhang et al, J clin Endocrin & metabolism, 1999, vol 84, no 10, p 3642-3646*).

[0009] Furthermore, Behre et al, 1999, relates to testosterone undecanoate preparations for testosterone replacement therapy such as testosterone undecanoate 125 mg/ml in teaseed oil and testosterone undecanoate 250 mg/ml in castor oil (*Behre et al, Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies. European J endocrin, 1999, 140, p 414-419*).

[0010] Intramuscular injections of 250 mg testosterone undecanoate and 200 mg MPA every month have been suggested for male contraception (*Chen Zhao-dian et al, Clinical study of testosterone undecanoate compound on male contraception. J Clin androl, 1986, vol 1, issue 1, abstract*). [0011] Wang Lie-zhen et al. report testosterone replacement therapy using monthly intramuscular injections of 250 mg testosterone undecanoate (*Wang Lie-zhen et al. The therapeutic effect of*
domestically produced testosterone undecanoate in Klinefelt syndrome. New Drugs Market 8: 28-32, 1991.

[0012] WO 95/12383 (Chinese application) relates to injectable compositions of testosterone undecanoate in vegetable oils selected from tea seed oil, sesame oil, arachis oil, olives oil and soyabean oil. The oil is optionally in admixture with benzyl benzoate. The compositions are injected monthly when applied for male contraception and substitution therapy.

[0013] US 4 212 863 Is a patent whlch_relates to a lipid formulation of steroids for oral or parenteral administration various oil carriers, optionally including benzyl benzoate, which is said to lower the viscosity of the lipid carrier and/or enhance the solubility.

[0014] Eckardstein and Niesclag, 2002, report the treatment of hypogonadal men with testosterone undecanoate, wherein physiologically relevant levels of testosterone may be achieved for an extended period of time upon initially injecting testosterone undecanoate four times in intervals of 6-weeks followed by subsequent injections of longer intervals (*Eckardstein and Niesclag, treatment of male*

hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks, J Andrology, vol 23, no 3, 2002)
[0015] However, it is well known that therapies with testosterone esters, such as testosterone undecanoate, still need to be improved in terms of achieving reliable serum testosterone levels in the physiologically acceptable range for a prolonged period of time. There is a need of providing reliable standard regimens acceptable for a broad population of men in need thereof, preferably regimens without the need of occasional control of serum testosterone levels, and regimens wherein steady state conditions are achieved within a shorter time period.

SUMMARY OF INVENTION

[0016] The present invention relates to injectable compositions comprising long-term acting testosterone esters for use in testosterone replacement therapy. Upon injecting the compositions, physiologically normal levels of testosterone in serum are reached within a short time period. Furthermore, the physiologically normal serum levels of testosterone are maintained for an extended period of time, without showing fluctuations in the hypogonadal range. The compositions are chemically stable with respect to the testosterone ester as well as physically stable with respect to the vehicle for a prolonged time.
[0017] Therefore, in a first aspect the present invention relates to a composition intended for injectable administration, such as by intramuscular injections, the composition comprises a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanotes, dodecanoates, tridecanoates, tetradecanoates and pentacanoates preferably testosterone undecanoate; and a vehicle, which comprises castor oil and a co-solvent.
[0018] Furthermore, in a second aspect the invention relates to a method of treating diseases and symptoms associated with deficient endogenous levels of testosterone in a man. For example methods of treating primary and secondary hypogonadism; hypophyseal diseases; symptoms of sexual dysfunction; symptoms of reduced muscle mass and muscle strength; symptoms of depressed mood; or symptoms of osteoporosis. The method comprises administering by injection a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates, such as testosterone undecanoate, according to a particular scheme comprising:

> i) an initial phase of 2 to 4 injecting a dose of said testosterone ester with an interval of 4 to 8 weeks between each administration, each dose being in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg; followed by
> ii) a maintenance phase of subsequent injecting a dose of said testosterone ester with an interval of at least 9 weeks between each subsequent administration, each dose is in an amount therapeutically equivalent to a dose of testosterone undecanoate of between 500 mg and 2000 mg.

(...)
DETAILED DESCRIPTION OF THE INVENTION

[0021] The present inventors provide, herein, standard methods resulting in superior pharmacokinetic profiles of testosterone in vivo. Physiologically normal serum levels of testosterone are achieved quickly after initiating the therapy with the testosterone preparations of the invention and reliable testosterone serum levels within the normal physiological range is maintained for an extended period of time. Advantageously, the standard methods reported herein, allows for significant prolonged intervals between injections, and the serum testosterone levels may not necessarily need to be controlled.
(...)
[0025] The present inventors have recognised that an effective depot effect in vivo of testosterone esters, such as testosterone undecanoate, is achieved when injecting the testosterone esters intramuscularly in a vehicle comprising castor oil and a suitable co-solvent. The co-solvent may lower the viscosity of the castor oil and then solve the problem with high viscosity of the castor oil

when being injected. On the other hand, the co-solvent may increase the diffusion rate of the testosterone ester, resulting in a lower depot effect following intramuscular injection.
(...)
[0029] As stated, the co-solvent of the vehicle is, at least in part, an essential element of the compositions of the invention. Such co-solvents may in general be defined by its capability of reducing the viscosity of castor oil, as determined by a Höppler viscosimeter.
(...)
[0038] The solubility of the testosterone esters may be affected upon adding a co-solvent to the castor oil vehicle. Probably the solubility may be improved. Thus, in some embodiments, the testosterone ester is completely dissolved in the composition, and in other embodiments the testosterone ester is partly dispersed in the composition. Preferably, the testosterone esters are fully dissolved in the vehicle. That is to say that no particles of testosterone may be detected by X-ray diffraction analysis.
(...)
[0040] The present invention provides compositions, wherein the co-solvent is present in the vehicle at concentrations ranging from 10 to 90 vol%. Preferably, the concentration of the co-solvent in the vehicle ranges between 15 to 85 vol%, more preferably between 20 to 80 vol%, such as between 45 to 85 vol% or 55 to 85 vol%.
(...)
[0042] It should be understood that intentionally the composition should not comprise another plant oil, such as for example tea seed oil. That is to say that castor oil is the only plant oil present in the composition or that castor oil makes up at least 50% by volume of the total content of the plant oil in the vehicle, such as at least 60%, 70%, 80% or 90% by volume.
(...)
[0046] In order for using single injections and low injections volumes, the concentration of the testosterone esters in the compositions need to be relatively high. Thus, a testosterone ester, such as testosterone undecanoate is in a concentration of 100 mg to 1000 mg per mL of the vehicle. In still interesting embodiments, the testosterone ester, such as testosterone undecanoate, is in a concentration of 130 to 750 mg per mL of the vehicle, more preferably of 150 to 500 mg per mL, most preferably of 175 to 400 mg per mL, such as about 250 mg/mL of the vehicle.
[0047] In order for using single injections and low injections volumes, the concentration of the testosterone esters in the compositions need to be relatively high. Thus, a testosterone ester, such as testosterone undecanoate is in a concentration of 100 mg to 1000 mg per mL of the vehicle. In still interesting embodiments, the testosterone ester, such as testosterone undecanoate, is in a concentration of 130 to 750 mg per mL of the vehicle, more preferably of 150 to 500 mg per mL, most preferably of 175 to 400 mg per mL, such as about 250 mg/mL of the vehicle.
(...)
[0061] The present inventors provide herein evidence for that upon applying a first injection interval of 6 weeks (injection of a first dose followed by a second dose 6 weeks after the first injection), the time until steady-state conditions is shortened. Thus, a maintenance phase may start already after 6 weeks of therapy. As further shown herein, the subsequent injection of testosterone undecanoate can be conducted using intervals of 10 weeks or 12 weeks between injections so as to achieve serum testosterone levels remaining well within the normal range of 10 to 35 nmol/l throughout the entire period between injections. Thus, an injection scheme resulting in reliable serum testosterone levels ranging from 10-35 nmol/L has been found.
[0062] The pharmacokinetic profile of the composition of the invention allows for extended periods between injections when steady state conditions is first achieved. Thus, in preferred embodiments of the invention, the maintenance phase comprises that the subsequent injections are conducted with an interval of 10 weeks between subsequent injections, preferably with an interval of 11 weeks, such as intervals of 12, 13, 14, 15 and 16 weeks between subsequent injections of the compositions of the invention.
[0063] The actual dose of testosterone ester being injected will also modify the depot effect of the compositions of the invention. Therefore, in suitable embodiments of the invention, the injected single dose of said testosterone ester is in an amount therapeutically equivalent to a single dose of testosterone undecanoate of between 750 to 1500 mg. Preferably, 1000 mg of testosterone

undecanoate is injected as a single dose or any therapeutically equivalent dose of another testosterone undecanoate of the invention.
(...)
Example 2

[0081] The therapeutic efficacy and safety of a formulation containing testosterone undecanoate 1000 mg in a vehicle of 4 mL of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume has been investigated in hypogonadal men. The formulation (4 mL, 1000 mg of testosterone undecanoate) was injected intramuscularly to the hypogonadal men according to the following scheme:
• initial phase comprising 4 injections of the formulation with intervals of 6 weeks between the injections.
• maintenance phase comprising injecting the formulation at intervals of 10 or 12 weeks between injections.
(...)
[0084] The results of this study allow for the following conclusion: Treatment with only 4 TU doses of 1000 mg i.m. per year was sufficient to restore physiological serum T levels in all 36 patients over most of the measurement times. This demonstrates that an injection interval of 12 weeks is adequate for most of the patients.

Example 3

Pharmacokinetic profile of compositions of the invention:

[0085] The pharmacokinetic profile of a formulation containing testosterone undecanoate (TU) 1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume was tested in hypogonadal men (having testosterone levels in serum of less than 10 nmol/I). An initial phase of two first intramuscularly injections of 1000 mg TU with 6-week interval between the two injections, followed by a maintenance phase of subsequent 3 intramuscularly injections of 1000 mg TU separated by an interval of 10 weeks between each of the injections. Then 1000 mg of testosterone undecanoate (TU) was injected intramuscularly every 12 weeks. 5 treatment periods were provided with an interval of 12 weeks between each injection.
[0086] The result from this study shows (see figure 1) that the treatment scheme resulted in testosterone levels (total levels) wherein the maximal and minimal levels are within the physiological acceptable range and no accumulation of testosterone is seen over time. Furthermore, the minimum testosterone levels (total levels) after 12 weeks do not fall below the lowest acceptable concentration of testosterone of about 10 nmol. The same was shown to apply for a treatment period of 14 weeks upon extrapolating the serum levels of testosterone. The study also demonstrated that injection of 1000 mg of TU in the above-mentioned formulation in intervals of 12 weeks between injections was efficient over a period of 14 weeks.

Example 4

[0087] Comparison of initial phases with 6 weeks between injections and 10 weeks between injections.
[0088] The pharmacokinetic profile of a formulation containing testosterone undecanoate (TU)1000 mg in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume was tested using two different regimens in hypogonadal men.
[0089] In regimen A, an initial phase of two first intramuscularly injections of 1000 mg TU with mean of 9.2-weeks (64.4 days) interval between the two injections, followed by a maintenance phase of subsequent intramuscularly injections of 1000 mg TU separated by an interval of a mean of 10.2 weeks (76.2 days) after second injection.
(...)
[0093] It appears that regimens including long-term intervals between injections, both with respect to the initial phase and maintenance phase, do not result in the sufficient levels of testosterone above 10

nmol over the entire period and up to the following injection (Regimen A). However, upon decreasing the interval between injections in the initial phase to 6 weeks, a reliable regimen is achieved, wherein sufficient testosterone levels are reinstated very fast and remains at levels above 10 nmol/l.

2.7. In these Dutch proceedings, Grünenthal relies on claims that are significantly limited compared to the claims as granted. The limited claims read in the original English language as follows:

1. A composition formulated for intramuscular injection as one single dose, said composition comprising 750 mg to 1500 mg testosterone undecanoate; and a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzyl benzoate.
2. The composition according to any of the preceding claims, wherein the vehicle comprises castor oil in a concentration of 25-40 vol%.
3. A pharmaceutical formulation containing 1000 mg testosterone undecanoate in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume.
4. Use of a composition as defined in any one of claims 1-2 in male contraception.
5. Use of testosterone undecanoate for the preparation of a medicament for treating primary and secondary hypogonadism in a man, said medicament is in a form for intramuscular injection as one single dose, and said medicament comprising 750 mg to 1500 mg testosterone undecanoate and comprising a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzyl benzoate, and wherein said treating comprises
   i) an initial phase of 2 or 3 injections of a single dose of said testosterone undecanoate with an interval of 4 to 8 weeks between each injection; followed by
   ii) a maintenance phase comprising subsequent injections of a single dose of said testosterone undecanoate with an interval of at least 9 weeks between each subsequent injection.
6. The use according to claim 5, wherein said primary hypogonadism is derived from testicular failure selected from the group consisting of cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy and toxic damage from alcohol or heavy metals.
7. The use according to claim 5, wherein said secondary hypogonadism is derived from idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury caused by tumours, trauma or radiation.
8. Use of testosterone undecanoate for the preparation of a medicament for treating diseases and symptoms associated with deficient levels of testosterone in a man who is in therapy with a progestin or a gonadotropin suppressive agent, said medicament is in a form for intramuscular injection as one single dose, and said medicament comprising 750 mg to 1500 mg testosterone undecanoate, and comprising a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzyl benzoate, wherein said treating comprises
   i) an initial phase of 2 or 3 injections of a single dose of said testosterone undecanoate with an interval of 4 to 8 weeks between each injection; followed by
   ii) a maintenance phase comprising subsequent injections of a single dose of said testosterone undecanoate with an interval of at least 9 weeks between each subsequent injection.
9. The use according to claim 8, wherein said deficient levels of testosterone in a man is such that the concentration of testosterone in serum is less than 10 nmol/l.

2.8. Below, the limited conclusions in the original English language are reproduced again, with *track changes* showing the changes from the conclusions as granted (underlined = added; crossed out is removed):

1. A composition formulated for intramuscular injection as one single dose, said composition comprising ~~a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoates750~~ mg to 1500 mg testosterone undecanoate; and a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzylbenzoate.
2. ~~The composition according to claim 1, wherein the testosterone ester is testosterone undecanoate.~~
3. ~~The composition according to claim 2, wherein the testosterone undecanoate is in a dose of 150 to 500 mg per ml.~~
4. 2. The composition according to ~~any of~~ the preceding claims, wherein the vehicle comprises ~~the~~ castor oil in a concentration of 25-40 vol%.
5. ~~The composition according to any of claims 1-3, wherein the co-solvent is in an amount ranging from 55 to 65 vol% of the vehicle.~~
6. ~~The composition according to any one of the preceding claims, wherein the co-solvent is benzyl benzoate.~~
7. 3. A pharmaceutical formulation containing J1~~,~~000 mg testosterone undecanoate in a vehicle of 4 ml of a mixture of castor oil and benzyl benzoate in a ratio of 1:1.7 by volume.
8. 4. Use of a composition as defined in any one of claims 1-2 ~~or a pharmaceutical formulation as defined in claim 7~~ in male contraception.
9. 5. Use of ~~a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoatestosterone~~ undecanoate for the preparation of a medicament for treating primary and secondary hypogonadism in a man, said medicament is in a form for intramuscular injection as one single dose, and said medicament comprising 750 mg to 1500 mg testosterone undecanoate and ~~comprisinges~~ a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzyl benzoate, and wherein said treating comprises
   i) an initial phase of 2 or 3 injections of a single dose of said testosterone undecanoate with an interval of 4 to 8 weeks between each injection; followed by
   ii) a maintenance phase comprising subsequent injections of a single dose of said testosterone undecanoate with an interval of at least 9 weeks between each subsequent injection.
10. 6. The use according to claim 95, wherein said primary hypogonadism is derived from testicular failure selected from the group consisting of cryptorchidism, bilateral testicular torsion, orchitis, orchidectomy, Klinefelter syndrome, chemotherapy and toxic damage from alcohol or heavy metals.
11. 7. The use according to claim 95, wherein said secondary hypogonadism is derived from idiopathic gonadotropin releasing hormone (GnRH) deficiency or pituitary-hypothalamic injury caused by tumours, trauma or radiation.
12. 8. Use of ~~a of a testosterone ester selected from the group of esters consisting of linear and branched nonanoates, decanoates, undecanoates, dodecanoates, tridecanoates, tetradecanoates and pentadecanoatestestosterone~~ undecanoate for the preparation of a medicament for treating diseases and symptoms associated with deficient levels of testosterone in a man who is in therapy with a progestin or a gonadotropin suppressive agent, said medicament is in a form for intramuscular injection as one single dose, and said medicament comprising 750 mg to 1500 mg testosterone undecanoate, and comprising a vehicle comprising castor oil in a concentration of 25-45 vol% and a co-solvent in an amount ranging from 55 to 65 vol% of the vehicle, wherein the co-solvent is benzyl benzoate, and wherein said treating comprises
   i) an initial phase of 2 or 3 injections of a single dose of said testosterone undecanoate with an interval of 4 to 8 weeks between each injection; followed by

ii) a maintenance phase comprising subsequent injections of a single dose of said testosterone undecanoate with an interval of at least 9 weeks between each subsequent injection.

13. 9. The use according to claim 108, wherein said deficient levels of testosterone in a man is such that the concentration of testosterone in serum is less than 10 nmol/l.
14. ~~The use according to claims 8-13, wherein the testosterone ester is testosterone undecanoate.~~
15. ~~The use according to any of claims 8 to 14, wherein said medicament comprises said testosterone ester in a 6-week dose of 500 mg to 2000 mg, a 9-week dose of 500 mg to 2000~~ mg, a ~~10-week dose of 500 mg to 2000 mg, an 11-week dose of 500 mg to 2000 mg, a 12-week dose of 500 mg to 2000 mg, a 13-week dose of 500 mg to 2000 mg, a 14-week dose of 500 to 2000 mg, a 15-week dose of 500 to 2000 mg or a 16-week dose of 500 mg to 2000~~ mg~~.~~
16. ~~The use according to claim 15, wherein said 6-, 9-, 10-, 11-, 12-, 13-, 14-, 15- and 16-week dose is of 750 mg to 1500 mg.~~
17. ~~The use according to any of claims 8 to 16, wherein the co-solvent is benzyl benzoate.~~

2.9. The uncontested Dutch translation of the limited conclusions reads:

1. Composition formulated for intramuscular injection as a single dose, which composition comprises 750 mg to 1500 mg testosteroneundecanoate; and a carrier comprising castor oil at a concentration of 25-45% by volume and a co-solvent at an amount of 55-65% by volume of the carrier, the co-solvent being benzyl benzoate.
2. Composition according to the preceding claim, wherein the carrier contains castor oil at a concentration of 25-40% by volume.
3. A pharmaceutical formulation containing 1000 mg testosterone decanoate in a 4-ml carrier of a mixture of castor oil and benzyl benzoate in a volume ratio of 1:1.7.
4. Use of a compound as described in one of the conclusions 1-2 in male contraception.
5. Use of testosteroneundecanoate for the preparation of a drug for the treatment of primary and secondary hypogonadism in a man, wherein the drug is in a form for intramuscular injection as a single dose, and said drug comprises 750 to 1,500 mg of testosteroneundecanoate, and a carrier, which comprises castor oil at a concentration of 25-45% by volume a co-solvent in an amount of 55 to 65% by volume of the carrier, wherein the co-solvent is benzyl benzoate, and wherein said treatment comprises
   i) an initial phase of 2 or 3 injections of a single dose of said testosterone decanoate with an interval of 4 to 8 weeks between each injection; followed by
   ii) a maintenance phase comprising follow-up injections of a single dose of said testosterone decanoate with an interval of at least 9 weeks between each follow-up injection.
6. Use according to claim 5, wherein the hypogonadism arose from testicular failure chosen from the group consisting of cryptorchidism, bilateral testicular torsion, testicular inflammation, orchiectomy, Klinefelter's syndrome, chemotherapy or toxic injury from alcohol or heavy metals.
7. Use according to claim 5, wherein the hypogonadism arose from idiopathic deficiency of gonadotropin-stimulating hormone (GnRH) or injury to the pituitary gland due to tumours, injury or radiation.
8. Use of testosteroneundecanoate for the preparation of a medicine for the treatment of diseases and symptoms associated with reduced testosterone levels in a man under treatment with a progestativum or a gonadotropin-suppressing agent, wherein the medicine is in a form for intramuscular injection as a single dose, and said medicine comprises 750 to 1,500 mg of testosteroneundecanoate, and a carrier,

comprising castor oil in a concentration of 25-45% by volume a co-solvent in an amount of 55-65% by volume of the carrier, wherein the co-solvent is benzyl benzoate, and wherein the treatment comprises
i) an initial phase of 2 or 3 injections of a single dose of said testosterone decanoate with an interval of 4 to 8 weeks between each injection; followed by
ii) a maintenance phase comprising follow-up injections of a single dose of said testosterone decanoate with an interval of at least 9 weeks between each follow-up injection.

9. Use according to claim 8, where the reduced testosterone level in a man is such that the serum testosterone level is below 10 nmo1/1.

2.10. Teva c.s. is part of the Teva Group, an international pharmaceutical company engaged in the manufacture and marketing of generic and innovative medicines.

2.11. On 19 December 2022, a Dutch marketing authorisation with registration number RVG 129459 was issued to Teva B.V. for a generic version of Nebido with the brand name Testosterone Teva. The SmPC of Testosterone Teva is almost identical to that of Nebido. Testosterone Teva is also approved as an ampoule/injection vial with 4 ml solution for injection containing 1000 mg TU in a castor oil carrier and the co-solvent BzBzo (in an amount of 500 mg/ml). Teva c.s. intends to market this product through Teva Netherlands.

2.12. By letters dated 7 February and 12 April 2023, Grünenthal informed Teva B.V. that a market launch of Testosterone Teva would infringe EP 208. Grünenthal asked Teva B.V. to confirm that it will respect EP 208 or to explain why Testosterone Teva does not infringe EP 208. There has been no response to this.

2.13. By decision of the German Bundespatentgericht of 1 February 2023, the German part of EP 208 was annulled, also in the form of several requests for relief that were before it due to lack of inventive step starting from Von Eckardstein (see 2.17 below). The requests for relief that were before it there differed from the limited claims relied on by Grünenthal in these proceedings. In particular, none of the relief applications before it there contained any limitation on the active substances (the esters) compared to the conclusions as granted. Grünenthal has appealed against that judgment.

2.14. In a letter dated 26 June 2023, the Minister of Health, Welfare and Sport announced that Nebido and Testosterone Teva will be designated as interchangeable medicines on Appendix 1A of the Health Insurance Regulations with effect from 1 October 2023, allowing health insurers to designate either of them as a preferred medicine to be reimbursed on a sole basis within that cluster of the drug reimbursement system.

2.15. By judgment of the High Court of Justice of England and Wales (Patents Court) of 24 July 2023, the English part of EP 208 was set aside at first instance. In that case, the patent as granted and an application for relief were before it (which differed from the limitation presented in these Dutch summary proceedings in that the quantity of BzBzo was not limited). The English court concluded:

i) The obviousness attack from von Eckardstein and the documents to which it cross-refers fails.
ii) All the claims of the Patent as proposed to be amended either conditionally or unconditionally are insufficient for lack of plausibility across their scope and therefore invalid.

2.16. By letter dated 24 August 2023, Teva. B.V., in response to the summons dated 7 February 2023, notified Grünenthal of its intention to dissolve Testosterone Teva to be included in the October 2023 update of the G-standard, to be published on 19 September 2023, and then to be offered in the Netherlands. Teva B.V. argues that this does not constitute an infringement of EP 208, because the Dutch part of EP 208 is invalid due to lack of inventive step and/or subsequent workability. It referred to the aforementioned German and English rulings.

2.17. The state of the art for EP 208 includes the publication by Von Eckardstein et al, "*Treatment of male hypogonadism with testosterone undecanoate injected at extended intervals of 12 weeks: a phase II study*", published in *Journal of Andrology, vol. 23, No. 3, May-June 2002* (hereafter Von Eckardstein). This publication is cited in [0014] of the patent.

2.17.1. Von Eckardstein's findings are summarised in the abstract as follows:

"ABSTRACT: This paper reports the result of an open-label, non-randomised clinical trial investigating the efficacy and safety of an injectable preparation of testosterone undecanoate (TU) dissolved in castor oil and given over a 3.2-year period. In a previous study we demonstrated that injections of TU every 6 weeks resulted in satisfactory substitution but a tendency toward testosterone accumulation. Here we investigate prolonged TU treatment at extended injection intervals in 7 hypogonadal men. Injections were given at gradually increasing intervals between the fifth and 10th injection, and from then on every 12 weeks. Steady state kinetics were obtained after the 13th injection. Well-being, sexual activity, clinical chemistry, prostate volume, and prostate-specific antigen (PSA) and serum hormone levels were monitored. Patients were clinically well adjusted throughout the study. Before the next injection, testosterone, dihydrotestosterone, and estradiol levels were mostly within the Germany normal range and showed a tendency to decrease with increasing injection intervals. Body weight, haemoglobin, serum lipids, PSA, and prostate volume did not change significantly during the 3.2 years of treatment. PSA levels were always within the normal limit. Maximal testosterone levels during steady state kinetics were measured after 1 week with 32.0 ±- 11.7 nmol/L (mean ± SD). Before the last injection, mean testosterone concentrations were 12.6 ± 3.7 nmol/L. Compared with conventional testosterone enanthate or cypionate treatment requiring injection intervals of 2-3 weeks and resulting in supraphysiological serum testosterone levels, injections of TU at intervals of up to 3 months offer an excellent alternative for substitution therapy of male hypogonadism."

2.17.2. Von Eckardstein's study includes the following about the preparation used:

"Testosterone Preparation
TU was obtained from Jenapharm GmbH & Co. KG, Jena, Germany. Each ampule contained 1000 mg TU dissolved in 4 ml castor oil. Single injections were administered with the total volume at one site intramuscularly into the musculus gluteus medius, taking care to perform injections slowly to avoid pain."

2.18. Also among the state of the art is a publication by C. Riffkin et al, "*Castor oil as a vehicle for parental administration of steroid hormones*", published in

Journal of Pharmaceutical Sciences, Vol. 53, No. 8, August 1964, 891-895 (hereafter Riffkin). In it, the following is reported:

in the abstract:

"Steroid hormones may be administered parenterally in high concentrations as oil solutions. In this form they exhibit a prolonged action and reduce the number of injections required. To accommodate the demand for increasingly greater concentrations of hormones in solution, castor oil in combination with other suitable oil-miscible solvents, has been found to fulfil a need. The development of several formulations together with the results of animal testing, as well as clinical trials in humans, attest to the acceptability of this oil for the purposes intended."

in table II:

TABLE II.—SOLUBILITY OF STEROIDS IN U.S.P. OILS AT 25°

Steroid	mg./ml. Castor Oil	mg./ml. Sesame Oil	mg./ml. Peanut Oil
17-Hydroxyprogesterone caproate	55.6	23.4	27.9
Testosterone	38.6	5.4	8.1
Estradiol valerate	60.6	16.1	18.8
Progesterone	52.0	22.9	23.5

Under "*Discussion*":

"Despite better solubility of steroids in castor oil, other cosolvents were necessary to dissolve the increasingly higher concentrations required by therapeutic regimens. Often these materials contributed additional advantages. For example, the addition of benzyl alcohol or benzyl benzoate to castor oil resulted in a lower and more favourable viscosity, making it easier to inject. Also, benzyl alcohol was an effective preservative and local anaesthetic."

3. The dispute

3.1. Grünenthal claims - in summary and omitting the provisional claims already decided in the interlocutory judgment - as far as possible enforceable:

1. an injunction to cease and desist (in)direct infringement of EP 208 in the Netherlands, in particular a prohibition to manufacture, offer, put into circulation, use, import or stock Testosterone Teva for that purpose;
2. a prohibition against acting unlawfully towards Grünenthal, in particular by refraining from inducing, permitting, approving, facilitating, promoting, or provoking related entities, third-party distributors and/or intermediaries to commit infringement, or knowingly profiting from such infringement, in particular by refraining from approving to use, or making available

of its marketing authorisations for Testosterone Teva, or use it itself to infringe;
3. imposition of a penalty of €100,000 for each day (part) that Teva c.s. fails to comply with the injunction and prohibition under 1 and/or 2 or of €10,000 for each infringing product;
4. order Teva et al. jointly and severally to pay the legal costs pursuant to section 1019h Rv, plus statutory interest;
5. setting the time limit under section 1019i Rv at six months.

3.2. Grünenthal bases its claims on the fact that Teva c.s. threatens to infringe EP 208 with its intended market launch of the generic drug Testosterone Teva, which falls within the scope of protection of (in these proceedings limited claims 1, 2 and 5 to 7 of) the Dutch part of EP 208.

3.3. Teva et al. put forward a defence seeking dismissal of the claims, ordering Grünenthal to pay the costs of the proceedings within the meaning of Section 1019h Rv.

3.4. Teva et al. argues that there is a serious, non-negligible chance that EP 208 will be overturned in proceedings on the merits for lack of inventive step and/or after-effectiveness.

3.5. The parties' contentions are discussed in more detail below, insofar as relevant.

4. The review

Powers

4.1. The interim relief judge has international jurisdiction to hear the claims under Article 4 Brussels I bis-Vo[3] , as Teva c.s. is domiciled in the Netherlands. Relative (and exclusive) jurisdiction follows from Article 80(2)(a) ROW.

Urgent interest

4.2. It is not in dispute that there is an urgent interest of Grünenthal in its claims , given the launch of Teva Testosterone in the Netherlands announced by Teva et al. in October 2023.

Limited conclusions

4.3. Grünenthal bases its claim in these proceedings solely on a limited set of claims. It does not rely on the patent as granted.

4.4. Teva et al.'s argument that Grünenthal cannot base its interlocutory injunction claim on limited claims that have no legal standing needs no discussion, as Grünenthal filed a waiver after the conclusion of the oral proceedings

[3] Regulation (EU) 1215/2012 of the European Parliament and of the Council of 12 December 2012 on jurisdiction and the recognition and enforcement of judgments in civil and commercial matters

submitted to the OCNL, requesting that it be entered in the patent register as a matter of urgency. The text of the Dutch part of EP 208 after that waiver, corresponds to the limited claims presented above in 2.7, 2.8 and 2.9. From the moment of registration of that deed, which the interim relief judge concludes from the public register happened on 15 September 2023, the limited text applies retroactively to the Netherlands vis-à-vis everyone (art. 63 ROW). The text therefore forms the basis for the injunction claim and for an assessment of validity in these interim proceedings.

Technical background

4.5. The following introduction to the technique of the patent is drawn from what was agreed in the English case about what constitutes '*common general knowlegde'* relevant to this case, to which the parties have referred in this case.

4.6. Testosterone is the most important male sex hormone and essential for the development of (primary and secondary) male sexual characteristics. Testosterone is of great importance for metabolism and energy metabolism and has a significant influence on mood, intellectual abilities, social and sexual behaviour. The natural serum concentration of testosterone is between 10 to 12 and 35 nmol/l. If a man's body (the testes and, to a lesser extent, the adrenal glands) does not produce enough testosterone, this is known as hypogonadism. In clinical practice, hypogonadism occurs if a man has a prolonged low testosterone level (less than 10 nmol/l) and physiological complaints such as decreased libido, infertility, erectile dysfunction, osteoporosis, muscle weakness, depression and sleep disturbances.

4.7. Hypogonadism can be treated by administration of testosterone, with the aim of keeping the serum concentration of testosterone constantly in the natural range. Because testosterone is rapidly broken down in the body, maintaining a high enough testosterone level with "regular" testosterone is only possible if it is administered very frequently. Therefore, testosterone is administered in the form of a *prodrug*, usually a testosterone ester. A testosterone ester is a testosterone molecule to which a non-polar carbon chain is attached by means of an ester compound. In the body, the ester compound is broken down, creating free testosterone that can perform its natural function. Testosterone esters can be administered orally, via patches, gels or injections. At the priority date, the most common treatment consisted of an intramuscular (hereinafter IM) injection containing testosterone esters (testosterone antagonist and testosterone cypionate) in a carrier. In this process, the testosterone esters are dissolved in an oily carrier. The oil serves to delay the release of the testosterone esters. The oil remains in the tissue for an extended period of time, in the form of a so-called depot containing the testosterone ester. The testosterone ester diffuses slowly from the carrier into the tissue and then into the blood, where the testosterone ester is hydrolysed (split into free testosterone and the acid) to form free (active) testosterone. The rate at which an oil deposit releases a testosterone ester depends on a number of factors, including the lipophilicity and viscosity of the carrier (which in turn depends on its composition and the concentration of its components), the lipophilicity, quantity and concentration of the testosterone ester, the volume of the injected formulation and the rate at which the oil disappears from the body. Lipophilicity refers to the ability of a substance to dissolve in a fatty environment (as opposed to hydrophilicity, which indicates solubility in water). Viscosity

concerns the viscosity of a substance. The higher the lipophilicity and viscosity of the carrier, the slower generally the release is, but the more difficult the testosterone ester generally dissolves in it. The maximum volume that can be acceptably injected (without too much discomfort) into a patient's *gluteus medius* (gluteus muscle) is around 2-4 ml, with 5 ml at the priority date being the maximum volume allowed for therapeutic use.

The patent

4.8. The patent covers formulations to treat, in brief and to the extent relevant, hypogonadism. To this end, it provides pharmaceutical compositions and therapeutic uses thereof. The description of the patent explained that the standard treatment of hypogonadism at the priority date consisted of the administration of IM injections of testosterone esters with relatively short carbon chains. That treatment had to be repeated every two to three weeks. The disadvantage of this was not only frequent doctor visits, regular painful injections but also complaints about fluctuations in serum testosterone levels.

4.9. The invention relates to providing compositions of testosterone esters in castor oil that provide long-term reliable and physiologically acceptable serum testosterone levels, in such a way that selection intervals after an initial start-up phase in a maintenance phase can be limited to injections at 12-week intervals. The patent teaches that those long intervals can be achieved by optimising the depot effect of the formulation, allowing the testosterone esters to slowly degrade to free testosterone, thereby achieving a natural serum testosterone concentration without fluctuations over a longer period of time.

Infringement defence: Dutch part not valid

4.10. Grünenthal argues that Teva et al. infringes claims 1, 2, 5, 6 and 7 of the patent as limited in this case for the Netherlands. That Testosterone Teva is covered by those claims, with the exception of claim 2, is not in dispute. However, Teva et al. argues that the claims of the patent are not valid. In particular, it argues that claim 1 is not valid due to lack of inventive step starting from Von Eckardstein. In the alternative, in case Grünenthal's argument holds that the skilled person would not arrive at the invention embodied in claim 1 without inventive labour, it argues that that claim is not post-effective 'based on the same reasoning' across the board. No added matter-wars have been raised against the claims in limited form.

4.11. First of all, Teva c.s. argued that the claims for injunctive relief in (the main proceedings of) these preliminary relief proceedings should be dismissed without further review, because the foreign judgments on the merits referred to (2.13 and 2.15), in which the German and British parts of the patent were nullified, mean that the test in preliminary relief proceedings that a serious, non-negligible chance exists that the Dutch part of the patent will be found invalid in proceedings on the merits has already been met. According to Teva et al, this is all the more true since the parties in the foreign proceedings put forward largely the same arguments as in the present proceedings on the basis of the same documents and that they are authoritative foreign courts.

4.12. This argument is not followed. Although decisions of foreign courts deciding on the merits have great authority, the Dutch judge in interlocutory proceedings is not bound by them and will have to form his own judgment on the nullity claims made. This is all the more the case when the basis and debate are different and the test to be used differs.

4.13. In this case, the interim relief judge reached a different outcome from foreign courts with regard to parallel patents. Firstly, what is important in this respect is that in the present proceedings - following the partial surrender by Grünenthal - a narrower patent is before us than in the German and English proceedings, with claim 1 being further limited, as explained below. Also, the present contentions and defences are not identical to those in the foreign proceedings; for instance, both parties have relied on different experts (statements), so that the debate also differs in substance. Furthermore, the test to be applied in the Netherlands does not seem entirely the same. In particular, the English judgment with regard to plausibility (see above under 2.15), is not the same as the test to be used in the Netherlands in this case, following the ruling of the Grand Board of Appeal (GKB) of the European Patent Office (EPO) of 23 March 2023 (G2/21)[4] in preliminary opinion for inventive step.

4.14. Teva et al.'s argument that it must be a s s u m e d on substantive grounds that there is a serious, non-negligible chance that the Dutch part of the patent will be found invalid in proceedings on the merits, also fails on preliminary grounds. This is explained below.

Conclusion 1 (not) inventive?

4.15. The interim relief judge will first discuss the primary inventive step attack on claim 1. A preliminary opinion that that claim is valid already justifies an injunction, so there is no interest in a preliminary opinion on other claims.

4.16. When assessing the inventive step, the interim relief judge will use with the parties, the so-called *problem solution approach* (hereinafter PSA) as a tool. This involves determining the technical effects of the differences between the features of the patent claim as granted and the closest prior art. Based on those technical effects, the objective technical problem is identified, i.e. the problem that needs to be solved to achieve the technical effects. It is then assessed whether the average person skilled in the art, taking into account his general know-how, would reach the solution according to the patent (the features of the patent claim) on the priority date without inventive step.

Conclusion 1

4.17. Claim 1 of the patent is significantly reduced after abandonment, by incorporation of subclaims 2, 3 (in part), 5 and 6 and features from the (original) description. On the basis of the subdivision into partial features set out below, the interim relief judge explains in which respects this is the case:

[4] EPO GKB, 23 March 2023, G2/21 (Sumitomo / Syngenta)

1.1. Composition formulated
1.2. for intramuscular injection
1.3. as a single dose, which composition includes
1.4. 750 mg to 1,500 mg testosterone decanoate; and
1.5. a carrier who
1.6. castor oil at a concentration of 25-45% by volume and
1.7. includes a co-solvent in an amount of 55 to 65 vol% of the carrier,
1.8. where the co-solvent is benzyl benzoate.

4.18. Whereas the conclusion as granted for the active ingredient claimed a broad group of testosterone esters, the conclusion after distance has been limited to one particular testosterone ester: testosterone undecanoate (TU), where testosterone is esterified with an acid (undecanoic acid) with an aliphatic carbon chain having 11 carbon atoms. Secondly, it was added that the composition was formulated as a single dose comprising 750 mg to 1,500 mg TU (characteristics 1.3 and 1.4). All this, Grünenthal argued undisputedly, finds basis in claim 3 as submitted and various parts of the application.

4.19. A further limitation relates to the carrier. The conclusion as granted concerned a carrier containing castor oil in a concentration of 25-45% by volume. In addition, it referred to an unspecified 'co-solvent'. In claim 1 after waiver, the claim was limited to a specific co-solvent, namely BzBzo, and in a volume percentage ranging from 55-65. Also with regard to these amendments (in partial features 1.7 and 1.8), it is not in dispute that a basis for this can be found in the patent as granted.

4.20. In summary, the composition of the formulations under protection in conclusion 1 after distance consists of three specifically named substances, namely:
-TU (750-1500 mg)
and a carrier, with the carrier comprising ('*comprising*'):
- castor oil (25-45% by volume) and
- BzBzo (55-65 volume%).

Thereby, in claim 1 before us here, the range for each substance (TU, castor oil and BzBzo) is limited to the '*most preferable*' range disclosed in the description of the application and of the patent specification:
- For TU, this follows from [0047]: '*most preferably of 750 mg to 1500 mg, such as 1000 mg*'.
- In [0040] it states: '(....) *the vehicle* [the carrier, vzr] *comprises the castor oil in a volume concentration ranging between 25 to 45 vol% or 25 to 40 vol%*'.
- At the end of [0042], the most desirable amount of the co-solvent is included, namely '*about 55 to 65 vol% of the vehicle'*.

4.21. Use conclusions 5 and 8 after distance have been similarly restricted in terms of formulation composition. In addition, a specific dosing regime has been added to those conclusions.

4.22. The parties disagree on the interpretation of the following: Teva et al. argue that the percentages claimed for the two components of the carrier leave room for the possible presence of other components (another co-solvent or co-

solvents) to 0-20 volume% of the carrier. Grünenthal countered that the skilled person does not find any indication of the presence of a (second) co-solvent in either the patent specification or the original application so that this possibility is purely hypothetical. In the preliminary view, the person skilled in the art, reading the patent specification with a '*mind willing to understand*', will not so understand the claimed that it is intended to add a second solvent. The description and the claims (as applied for, granted and limited) always refer to '*a vehicle comprising castor oil and **a** co-solvent*' [emphasis added, Provisional Judge]. The subject matter expert could also understand the claimed differently, for instance so that the most limited range for castor oil disclosed in the application is too wide at the lower end in combination with the most limited range for a co-solvent (see 4.20) to which that conclusion as it is before us is limited, and those most limited ranges do not align (making 25-35 vol% castor oil in fact not possible).

Subject person

4.23. In these interim proceedings, there has been no subject of debate as to who should be considered the relevant average skilled person for the technique covered by this patent (hereinafter the skilled person) on the priority date. The interim relief judge assumes, with the German and English courts, that the subject matter expert in this case is a team consisting of a clinician (such as a urologist), a formulation expert and a pharmacologist (with knowledge of pharmacokinetics).

Nearest state of the art: Von Eckardstein

4.24. It is not in dispute that Von Eckardstein (see 2.17) should be considered the closest state-of-the-art in PSA application. That scientific publication presents the results of a long-term (more than three years) clinical trial (a phase-II study), which investigated the results (including serum testosterone levels) of administering 1000 mg TU in a castor oil carrier by way of IM injection as testosterone replacement therapy in the treatment of hypogonadism in seven men. The patients were treated with IM injections given at injection intervals of up to 12 weeks as follows. After a *washout phase* of at least 4 weeks prior to the first TU IM injection, 4 injections were administered at 6-week intervals in a start-up phase. Thereafter, the interval between injections was gradually increased and from the 10e injection onwards, the interval between injections was a maximum of 12 weeks.

4.25. Von Eckardstein concludes that extending the intervals up to 12 weeks in these patients appears possible with (maintenance of) physiologically acceptable serum testosterone levels[5] throughout the interval. The compound used with TU, allows longer injection intervals (up to 12 weeks) compared to conventional testosterone substitution therapies, which generally used testosterone esters with short carbon chains and with only 2 or 3 weeks between injections. T h e abstract in the headline of the publication expressed this as follows:

[5] That is, within the range of natural serum testosterone concentrations mentioned in 4.6.

Compared with conventional testosterone enanthate or cypionate treatment requiring injection intervals of 2–3 weeks and resulting in supraphysiological serum testosterone levels, injections of TU at intervals of up to 3 months offer an excellent alternative for substitution therapy of male hypogonadism.

And at the end of the *discussion* in the publication, it states:

In summary, results of this trial show that in an injectable form, TU is a highly interesting alternative to the currently most widely used injectable preparations, TE and TC. When applied at appropriate intervals of 10 to 12 weeks, TU injections by and large avoid supraphysiological testosterone levels, and their unwanted side effects.

4.26. About the composition of the injections, Von Eckardstein records that each ampoule contains 1000 mg of TU dissolved in 4 ml of castor oil and that the entire volume of an ampoule was administered at once (see 2.17.2).

4.27. The research in Van Eckardstein builds on two previous studies, viz:
- Behre[6] (Behre et al, 1999), in which the pharmacokinetics of a single injection of TU dissolved in castor oil was compared with the pharmacokinetics of a single injection of TU dissolved in tea seed oil (cited in the patent [0009]).
- Nieschlag[7] (Nieschlag et al, 1999), in which 4 injections of the same formulation as in Von Eckardstein were administered at 6-week intervals.

Difference characteristics

4.28. In Von Eckardstein, the precise (composition of the) formulation of the TU preparation that achieved physiologically acceptable serum testosterone levels for 12 weeks was not revealed. The difference characteristics between what Von Eckardstein teaches about the composition and what was stated in (limited) Conclusion 1 under protection are tabulated below. Given the explanation given above in 4.22, there is no reason to add the possibility of a second co-solvent for the carrier, as Teva c.s. argues.

Von Eckardstein	**EP 208 (limited conclusion 1)**
4 ml for IM injection as 1 single dose	for IM injection as 1 single dose
1000 mg TU	750-1500 mg TU
castor oil	25 - 45 vol% castor oil
	55-65 vol% BzBzo

[6] Behre et al, Intramuscular injection of testosterone undecanoate for the treatment of male hypogonadism: phase I studies, European Journal of Endocrinology (1999) 140, 414-419

[7] Nieschslag et al, Repeated intramuscular injections of testosterone undecanoate for substitution therapy in hypogonadal men, Clinical Endocrinology (1999), 51, 757-763

4.29. The parties largely agree on the difference characteristics. Grünenthal only argues that with the passage '*1000 mg TU dissolved in 4 ml castor oil*' [see 2.17.2] Von Eckardstein discloses a precise formulation consisting exclusively of 1000 mg TU in 4 ml pure castor oil (250 mg/ml). The high viscosity of castor oil (600-800 mPa-s), which is easy to look up or is already known to the person skilled in the art, implies that the relevant person skilled in the art, including a pharmacologist and a formulation expert, would understand that at least one co-solvent is needed to arrive at a realistic usable formulation. This has been explained by Prof , expert of Teva c.s. (hereinafter .However, this can also be inferred from the statement of Grünenthal's own expert, Prof. (submitted as production EP37):

"It is not impossible s (such as castor oil) intramuscularly serve, although this may be more difficult and painful for the patient." (marginal 45, first sentence, underlining provision judge)

and

"I noted that Professor assumes that the maximum viscosity for intramuscular injection is 100 mPa.s. That seems to me to be on the low side. The Herzfeldt textbook, for example, describes a maximum of 200 mPa.s. (...) A higher viscosity does not make injection impossible. At very high viscosity, injection becomes more difficult and painful, but it can be, and does happen, even in a therapeutic setting." (marginal 39)

4.30. Although it is disputed that the upper viscosity limit of a solution that is practically usable for IM injection mentioned by is 100 mPa-s, the upper viscosity limit of around 200 mPa-s mentioned by him with reference to a textbook is also far below the above-mentioned higher viscosity of pure castor oil (600-800 mPa-s) - confirmed by him (EP37, marginal 37) - by at least a factor of three. The subject would therefore not expect that seven patients would have been treated with such (difficult and painful) injections for more than three years, especially as Von Eckardstein records under '*Results'*: '*Injections were well toletarated by all men except one* (...)'.

Technical impact difference characteristics

4.31. The parties dispute whether the technical effect claimed by Grünenthal, namely the achievement of constant physiologically acceptable serum testosterone levels during the longer intervals revealed in Von Eckardstein with the compositions claimed in Conclusion 1 under protection (in short, 'that it works', hereinafter also referred to as 'the improved depot effect'), may and/or should be included as a technical effect of the difference characteristics, and therefore in the formulation of the objective technical problem.

4.32. Teva c.s. argues that this technical effect should not be included. According to it, the technical effect of the difference features is only the provision of (alternative) TU compositions (Conclusion of Reply margin 5.66). The effect of the improved filing effect, it argues, should not be included because this effect is not '*derivable*' for the subject matter expert across the full breadth of the conclusion from the

application. It relies on judgments of the TKB from 1995 (Agrevo[8]), of the Court of Appeal of The Hague from 2017[9] and on the aforementioned GKB judgment G2/21. According to Teva, it follows that it is not sufficient to show evidence in the patent of one formulation when ranges are claimed. The skilled person must be able to infer from the application that the technical effect claimed is actually realised for all possible formulations covered by the scope of protection of the claim.

4.33. Grünenthal's position is that the alleged technical effect may be taken into account. It argues that the bar for this in the context of inventive step is low, as confirmed in G2/21, and that what matters is only whether the person skilled in the art will be able to deduce from the application that this effect occurs, which is the case here. In doing so, Grünenthal said, it is not necessary to prove unequivocally that the conclusions 'work' across the board. Including evidence in the application that at least one compound works is sufficient except in 'extreme cases', which are not at issue here, at least after the limitation of the conclusion. In its view, the burden of proof that it is not inferable that it does not work across the full breadth of claim 1 lies with Teva et al.

4.34. The interim relief judge first of all stated that it is not in dispute that the alleged technical effect ('that it works') is not part of claim 1 as a (sub)characteristic. According to the text of the conclusion (after distance), the pharmaceutical compositions put under protection there require only that they are formulated 'for intramuscular injection as a single dose'. That those formulations also work, i.e. have the effect of enabling the intervals described in Von Eckardstein to be achieved while maintaining acceptable levels of testosterone, does not form part of claim 1 as a characteristic (other than in use claims 5, 6 and 7, which Grünenthal also bases its claims on).

4.35. In assessing whether the alleged technical effect in this case can be attributed to the difference features and may or should be taken into account in the determination of the objective problem definition, the interim relief judge and the parties seek in part to follow the recent authoritative ruling of the GKB. In G2/21, the GKB assessed when a patentee may rely on a technical effect achieved thereby in assessing the inventive step of his invention. According to the GKB's order, this is the case:
"if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention". [10]

4.36. Elsewhere in the judgment (paragraphs 72, 87, 93 and 94), instead of '*would derive*', the GKB also uses the terms '*derivable*', '*would understand*' and '*would consider*'. In the preliminary view, these always mean the same thing, and the test, translated into Dutch, amounts to the following:

[8] Technical Board of Appeal of the EPO, 12 September 1995, T-939/92 (Agrevo)
[9] Hague Court of Appeal 7 November 2017, ECLI:NL:GHDHA:2017:4029, r.o. 4.16
[10] Page 68 of the decision. G2/21 was recently explained by the Court of Appeal of The Hague in summary proceedings: Court of Appeal of The Hague 15 August 2023, ECLI:NL:GHDHA:2023:1593 (BMZ/Sandoz, aka the apixaban case)

Would the average person skilled in the art, using his general expert knowledge on the priority date, understand from the original application, or at least is inferable to him, that the alleged technical effect is encompassed by its technical doctrine and embodies the same invention revealed therein.

4.37. It does not follow from G2/21 that the application must include evidence that the alleged technical effect actually occurs or that this is made plausible in the application. Furthermore, the GKB has indicated in paragraph 95 of G2/21 that the 'rather abstract' criteria it set out in G2/21 must be *fleshed out* in a concrete case based on the specific circumstances of the case. This involves establishing what is necessary for the average practitioner to be able to infer from the application that the alleged technical effect was encompassed by its technical doctrine. That depends on the specific circumstances of the case.

4.38. In this case, in the preliminary view, the person skilled in the art will readily infer from the application that the technical effect claimed by Grünenthal is encompassed by its technical doctrine and embodies the same invention disclosed therein. Indeed, that technical effect is expressly and specifically mentioned as the primary object of the patent, including in the application. This already follows from the title, in the Dutch translation: *Processes and pharmaceutical compositions for reliably establishing acceptable levels of testosterone in serum*. It is then explained in [0001] of the patent specification that this relates to acceptable serum testosterone levels over an extended period of time, and in [0016] that the injectable testosterone esters used in the invention achieve physiologically normal testosterone levels within a short period of time that are maintained over an extended period of time, without fluctuations in the normal physiological range. It also follows from the '*detailed description of the invention*' in [0021] that (the processes and) preparations according to the invention rapidly lead to physiologically normal serum testosterone levels that are maintained for longer periods of time, allowing significantly longer injection intervals. These paragraphs also appear in the application. The provision of processes and preparations having the aforementioned effect/operation, should t h e r e f o r e be regarded as the technical teaching (aka the invention idea) of EP 208.

4.39. It is also significant that (the application for) this patent includes in its description (clinical) evidence that a formulation falling within the scope of claim 1 achieves the claimed technical effect. The patent specification includes trials and their results (*examples* 2, 3 and 4, see 2.6, conclusion), which tested the therapeutic efficacy, safety and pharmacokinetic profile. Thereby, for one particular compound, it has been shown that it achieves (in the treatment of hypogonadism) longer interjection intervals while maintaining physiologically acceptable testosterone levels. The composition with which those trials were conducted contains 1000 mg TU (250 mg/ml) in a carrier of (exclusively) castor oil and BzBzo in the ratio 1:1.7 in a volume of 4 ml. This corresponds to volume percentages of castor oil and BzBzo of 37% and 63%, respectively. This composition, as mentioned, falls within the scope of conclusion 1 and is also separately under protection in conclusion 3.[11]

[11] That conclusion was not invoked in this case (nor was its invalidity argued

4.40. The foregoing is not in dispute. However, Teva et al. argue that since the claim relates to ranges and not to a single composition or a single substance[12] , the alleged technical effect should only be taken into account if the person skilled in the art will infer from the patent specification that the technical effect occurs over the full breadth of the claim. Whatever the case may be, certainly for the limited claim 1, that condition is met in the preliminary view. The technical doctrine of the patent is aimed at providing formulations that work, i.e. with the alleged technical effect. Accordingly, the skilled person can infer from the patent specification that the formulations disclosed in claim 1 after waiver achieve the effect that the disclosed formulations allow longer injection intervals (after a start-up phase), while maintaining the intended serum testosterone level. In doing so, he has no reason to think that this will not be the case over the full breadth of the limited ranges, or at least that has not been made plausible by Teva et al. The only issue is that, for the average person skilled in the art using his general professional knowledge on the priority date, it would be out of the
application is *derivable* that the alleged technical effect is encompassed by its technical doctrine and embodies the same invention disclosed therein. Proof is not required. Based on his general professional knowledge, the person skilled in the art knew on the priority date what factors affect the deposit effect and therefore the longer efficacy of the formulated compositions after giving an injection (see 4.6 and 4.7). What was known to him on that account does not, in the preliminary view, make the subject person, given the relatively limited ranges in conclusion 1 (after distance), think that a formulation that is within the ranges, or that a substantial part of the formulations that are within the ranges, would not work. This has also not been argued by Teva et al in any substantiated way.

4.41. Therefore, in applying the G2/21 test when assessing the inventive step of a claim in which the technical effect is not included as a feature, in the preliminary view, contrary to Teva c.s.'s argument with reference to the Agrevo case of the TKB[13] , it is not necessary for the patentee to provide proof, or make it plausible in summary proceedings, that the technical effect works with at least the majority of the claimed compositions. This would, for the time being, only be different if Teva c.s., had made a sufficiently substantiated plausible case that the skilled person will not infer from the application, or will have reason to doubt, that this technical effect (the improved filing effect) occurs across the full breadth of claim 1 after distance. After all, Teva et al. have the duty, adjudicating provisionally, to allege this and make it plausible in preliminary relief proceedings.[14] To this end, Teva et al. argued (exclusively) on the basis of statements of its experts that it is not credible for the professional that the formulation using the maximum claimed amount of 1,500 mg TU will have the technical effect, because this amount of TU cannot be dissolved in 4 or (max.) 5 ml (the maximum acceptable volume, see above under 4.7) of castor oil and BzBzo (which the court in preliminary relief proceedings assumes at room temperature). Grünenthal argued that the conclusion does not require that the entire amount of TU is dissolved, and that also a composition with 1,500 mg of TU in 4 ml is expected to have an improved depot and therefore the claimed effect, regardless of whether part of the TU is not dissolved. Here,

[12] as in the facts underlying the recent interlocutory decision of the Court of Appeal of The Hague in which G2/21 was applied, the apixaban case, see footnote 10
[13] Technical Board of Appeal of the EPO, 12 September 1995, T-939/92 (Agrevo)
[14] Cf Hague Court of Appeal 7 November 2017, ECLI:NL:GHDHA:2017:4029, r.o. 4.16

Teva cs insufficiently opposed. Teva cs. has not put forward any other arguments to make it plausible that the skilled person will doubt whether the technical effect is achieved over the full ranges. In addition, it has not submitted (or offered to submit) any trial showing that a compound that falls within conclusion 1 after distance would not work. On the contrary, the tests it submitted concerning the solubility and viscosity of TU in carriers containing various combinations of castor oil and BzBzo show the opposite. These show that even with a carrier composition that falls outside the range (60% castor oil and 40% BzBzo, a composition in which the person skilled in the art would expect TU's solubility to be lower and its viscosity higher - thus expected to have a better depot effect - than in the inverse 40/60 ratio, which does fall within the range of the conclusion), TU is soluble therein in the desired amount (just over 250 mg/ml) and its viscosity is also acceptable at 113 mPa-s. Admittedly, the time to carry out extra tests was (too) limited in these preliminary relief proceedings, but in the German and English proceedings on the merits, which had been pending for much longer, such tests have not been submitted by Teva et al. as far as is known. However, it should have been expected to come up with more to make its position plausible that the skilled person would expect, based on its general professional knowledge, that some of the claimed formulations would not work.

4.42. On the other hand, Grünenthal pointed to '*post-filed evidence*' that supports her view that the technical effect is obtained across the board. These are compounds for which it is established that they satisfy the technical effect because they are on the market as (approved) drugs. This is primarily Nebido (see 2.2). Therein, a composition is revealed of a 4 ml solution for injection containing 1000 mg TU (250 mg/ml) dissolved in a castor oil carrier and 2000 mg (500 mg/ml) BzBzo. The parties agree that this corresponds to approximately 40.5 vol% castor oil and 59.5 vol% BzBzo. The second formulation proven to work is marketed in the US under the name Aveed and has the following composition: 3 ml solution for injection containing 750 mg TU (250 mg/ml) dissolved in a carrier of 1500 mg BzBzo (59.5 vol%) and 885 mg castor oil (40.5 vol%). In this case, there is post-application evidence from which it follows that the claimed effect actually occurs in vivo in two formulations (other than those disclosed in the patent specification *examples*) that fall within the scope of claim 1. This confirms what is inferable from the patent specification.

4.43. The conclusion from the foregoing is that the claimed technical effect - namely, the achievement of constant physiologically acceptable testosterone levels during the longer intervals disclosed in Von Eckardstein - is part of the difference features because it is '*derivable*' for the person skilled in the art from the application and embodied in the claimed formulations according to the restricted text, which formulations were also part of the invention disclosed in the original application.

The objective technical problem

4.44. The above leads to the conclusion that the technical effect may be included in the formulation of the objective technical problem. The objective technical problem starting from Von Echardstein is then, in view of the above: '*providing a TU formulation containing 1000 mg TU in a carrier containing castor oil, suitable for IM*

injection where stable physiologically acceptable serum testosterone levels are achieved and maintained when administered at longer injection intervals (at least as long injection intervals as in Von Eckardstein)'. There is no substantial dispute about this, if it is assumed that the alleged technical effect should be included.

Does the subject person without inventive labour arrive at the matter of conclusion 1 starting from Von Eckardstein?

4.45. Starting from the objective technical problem formulated above, it must then be assessed whether, without inventive labour, the skilled person would arrive at the invention embodied in claim 1 (after distance).

4.46. Teva c.s. argues that there is no inventive step because the person skilled in the art, trying to make an effective TU formulation in castor oil with a long-lasting depot effect from Von Eckardstein, arrives at the subject matter according to claim 1 without an inventive step. Teva et al. describe a number of steps that the person skilled in the art would successively take to arrive at the invention without any inventive step. As it rightly submits, the fact that a number of steps must be gone through does not in itself preclude the conclusion that the outcome is obvious. According to settled case-law, no inventive step can be assumed in a case where several successive steps are required in order to solve the objective technical problem, if and to the extent that the taking of each step was in itself obvious to the average person skilled in the art, having regard to what he had achieved in the preceding step and what else he had to do in order to ultimately arrive at the solution.[15]

4.47. According to Teva et al, the skilled person would routinely go through the following steps in arriving at the invention.

1. Conclude that the carrier of the formulation revealed in Von Eckardstein not only consists of castor oil but also contains a co-solvent.
2. Searching for a co-solvent and ending up with BzBzo without inventive labour.
3. To determine the appropriate ratio of castor oil and BzBzo so that 1000 mg TU can be dissolved in it and a suitable viscosity achieved. In doing so, the subject would arrive at a ratio of 40 : 60 volume% of castor oil and BzBzo, respectively, through routine tests.
4. Routinely conduct animal experiments and extrapolate their results to humans.

4.48. Grünenthal has disputed, with reasons, that the individual steps, and the sequence of those steps, are obvious. That defence succeeds: in the preliminary opinion of the interim relief judge, the skilled person would not have arrived at a claimed formulation by means of these steps without inventive labour. To this end, the following is reasoning.

4.49. It has already been discussed above (in 4.29 and 4.30) that the first step is indeed obvious, given the viscosity of castor oil. On top of this, the subject person, to Teva et al. rightly argue, can establish with a simple solubility test that 1,000 mg of

[15] Cf Hague Court of Appeal 27 August 2019, ECLI:NL:GHDHA:2019:3155, para 4.15

TU cannot be dissolved in 4 ml of pure castor oil, while Von Eckardstein mentions dissolving that amount in that volume.

4.50. In the second step, however, in the preliminary view, the nullity claim fails, firstly because it is not clear why the person skilled in the art would choose only one co-solvent, and that is BzBzo, because, as Grünenthal argued, BzBzo is not, at least not the only, obvious possibility. Teva c.s. reasoned that the subject matter expert would infer that BzBzo is a suitable co-solvent from Riffkin's publication and from an overview of the composition of similar formulations of hormone esters known on the priority date (it claims) mentioned by [redacted] . Moreover, Von Eckardstein itself would contain a pointer to BzBzo as a suitable co-solvent, as it refers to the (pre)clinical studies of Partsch and Zhang, which used an injectable TU formulation containing "*250 mg of the ester in 2 ml of tea seed oil with 15% benzyl benzoate*".

4.51. However, whether BzBzo is a 'suitable solvent' is not the test. At issue is whether the subject matter expert, when answering the formulated problem assuming Von Eckardstein, would without inventive labour arrive at the solution of the problem as reflected in the conclusion. This is not the case, at least not without *hindsight*. If the subject would come across Riffkin at all, as Teva et al argue and Grünenthal dispute, that publication teaches him that castor oil is a suitable carrier for the administration of hormone injections. Indeed, in Riffkin, the suitability of castor oil as a carrier was specifically examined. However, that publication did not examine the suitability of this carrier specifically for the hormone testosterone or of testosterone esters (although it did show the solubility of testosterone in various oils, including castor oil, see 2.18). The results of the suitability of castor oil as a carrier for esters with short carbon chains of two other hormones was published therein, but neither stated nor showed that they have the same or similar solubility profile as TU. The subject person would not extrapolate those data with expectation of reasonable success to an ester of another long-carbon-chain hormone. In Riffkin, BzBzo and benzyl alcohol are further revealed as constituents of the carrier besides castor oil, almost always used in combination. Again, this does not constitute a pointer to the choice of only BzBzo as a co-solvent for TU in castor oil.

4.52. Nor do the other arguments of Teva et al. make clear why the person skilled in the art *would* (could not) choose BzBzo as sole co-solvent. The Court in preliminary relief proceedings ignored the argument that Von Eckardstein would contain a pointer to BzBzo as the (sole) co-solvent, as this was a reference to a sentence that was included in another document, Partsch and Zhang, and not in Von Eckardstein. Moreover, that sentence, if the subject matter expert were to encounter it at all, teaches that BzBzo can be used as a co-solvent alongside '*tea seed oil*'. Teva et al did not explain why this is relevant to the subject person and would lead him/her to combine castor oil with (only) BzBzo for TU. Also, the six commercial formulations[16] of hormone esters mentioned by (expert [redacted] of) Teva c.s. that were available as medicines on the priority date would not, contrary to Teva c.s.'s contention, simply lead the subject to choose only BzBzo as a co-solvent. Most of those approved medicines are short-chain hormone esters. Not

[16] Mentioned in the table in paragraph 5.87 of the Conclusion of Reply

in dispute is that the active ingredient and, in particular, also the type of ester (i.e. the length of the carbon chain of the acid with which it is esterified) also influence the effect of the deposit (because, among other things, lipophilicity and viscosity). Teva et al did not make a plausible case that the subject matter expert would extrapolate those data to TU without further ado. Furthermore, in half of the cases cited, the hormone esters available as drugs were dissolved in a formulation containing three components; in addition to castor oil and BzBzo, benzyl alcohol. Therefore, it is not clear why, based on those existing formulations, the subject person would choose a castor oil carrier with (only) BzBzo as a co-solvent for TU.

4.53. Even the third step, in which, if the person skilled in the art had already arrived at the choice of BzBzo as sole solvent, the correct ratio of castor oil to BzBzo must be determined so that 1 000 mg of TU can be dissolved in it and at which a suitable viscosity and depot function can be achieved, requires inventive work in the preliminary view. Grünenthal disputes that these are routine tests, and that the person skilled in the art would choose these tests, especially since all the formulations with castor oil from the prior art referred to by Teva et al do not reveal ratios that fall within the ranges claimed in Conclusion 1. There is, as Grünenthal has argued, no pointer in the prior art that points the practitioner to the 40/60 carrier that Teva cs claims he *would* routinely arrive at. The only commercially available compound with that ratio was for an entirely different hormone (Proluton depot) for a different application. Compounds with active ingredients more similar to TU have different carriers. In Riffkin, the percentage of BzBzo is always below 50%, i.e. outside the claimed range. Also, the listed formulations approved for therapeutic use consistently contain more castor oil than BzBzo, with one exception containing 41% castor oil. Thus, based on the known carriers, the subject person would rather choose a carrier with 60% castor oil and 40% BzBzo than the other way around.

4.54. Teva et al's contention that the subject person routinely arrived at the 40% castor oil to 60% BzBzo ratio by doing simple solubility and viscosity studies, testing a range of formulations with different ratios of castor oil and BzBzo, is therefore rejected. From a number of, by Teva
c.s. consulted, tests would show that the subject would thereby arrive at formulations with a carrier in the ratio of 60:40 or 40:60, with a preference for the 40:60 carrier that has a slightly lower viscosity and is thus more pleasant for patients to inject. However, this is just a question. Only viscosity and solubility have sufficient predictive value for the efficacy of the depot *in vivo*. Grünenthal pointed out that the person skilled in the art knew on the basis of his general professional knowledge that more vol% BzBzo would lead to lower viscosity and lipophilicity and that he would therefore expect that a carrier with more BzBzo would lead to faster release of TU and thus to a reduced depot effect, so that a this correctly points away from the invention.

4.55. It is then also provisionally very questionable whether, without inventive labour, the subject matter expert would reach the fourth step, testing 1,000 mg of TU in a carrier of 40 vol% castor oil and 60 vol% BzBzo in animal models, which Teva et al argue and Grünenthal dispute are routine. Grünenthal also pointed out that extrapolating the results of animal tests to humans in oil deposits is difficult, which its expert [redacted] endorses.

4.56. The foregoing leads to the conclusion that, starting from Von Eckardstein, the subject matter expert would not, in preliminary judgment, reach the matter of claim 1 (after waiver) without inventive labour.

Concluse 1 (not) after-work?

4.57. Teva et al. argued in the alternative, in case the inventive step does not succeed, that claim 1 would not be fully post-actualisable in that case. It explained this by using the example already mentioned that 1500 mg TU is not soluble in 5 ml carrier. This has been disputed by Teva et al. It pointed out, among other things, with reference to its expert [redacted], that conclusion 1 does not require that the quantity of TU is completely dissolved. The possibility that it is partly a suspension is therefore not excluded. In the preliminary view, this defence by Grünenthal succeeds. Other non-after-effectiveness arguments have not been put forward, or not substantiated, by Teva et al. The sentence that conclusion 'according to the same reasoning' (see 4.10) [as with respect to inventive step] the conclusion is not post-workable, cannot, for the time being, succeed without further explanation.

Final sum

4.58. Therefore, in the preliminary opinion, there is no serious, non-negligible chance that claim 1 will be found invalid in proceedings on the merits due to lack of inventive step. Since it is not in dispute that the marketing of Testosterone Teva will infringe that claim, the claim for an injunction is ready to be allowed. The alleged invalidity of the other claims needs no discussion at this stage.

Claims (in the main action)

Infringement ban

4.59. In view of the above, the claimed injunction will be granted. The ban on infringement will be imposed on Teva B.V. and Teva Nederland B.V. Teva c.s. has explained that the operating company Pharmachemie is not involved in the planned marketing of Testosterone Teva, so that the claims in respect of it will be dismissed, which has not, or at least has not been sufficiently refuted by Grünenthal.

Prohibition of unlawful conduct

4.60. Grünenthal also seeks an injunction against unlawful conduct to prevent Teva c.s. from performing acts that might not qualify as patent infringement, such as cooperating with third parties to market Testosterone Teva in the Netherlands and using and making available to third parties its Dutch marketing authorisation. It is impossible to see what interest Grünenthal has in doing so now that Teva
B.V. and Teva Nederland B.V. is already prohibited from infringement, or at least, Grünenthal has not, or at least has not sufficiently, explained this. This claim is therefore dismissed.

Penalty

4.61. A penalty payment will be imposed as an incentive to comply with the infringement order. The penalty payment claimed will be mitigated and capped as after.

Litigation costs

4.62. The parties entered into a litigation costs agreement. Under this, the successful party will be awarded €40,000. The parties' agreement on costs relates to all costs of these proceedings, i.e. both in the provisional claim and in the main action. Grünenthal counts as the (mainly) successful party in both the provisional claim and the main action. As the claims against Pharmachemie are dismissed, Teva B.V. and Teva Nederland (in the main action and in the provisional provision) will be ordered jointly and severally to pay Grünenthal the aforementioned amount.

Time limit article 1019i Rv

4.63. The interim relief judge will set the deadline for filing a claim in the main action as referred to in Section 1019i Rv at six months from today.

5. The decision

The preliminary relief judge

5.1. orders Teva B.V. and Teva Nederland B.V. with immediate effect to cease and desist from any direct or indirect infringement of the Dutch part of EP 208 in the Netherlands, and in particular to cease and desist from producing, offering, bringing into circulation, using, importing or stocking Testosterone Teva for that purpose, such under penalty of forfeiture of an immediately payable penalty of € 50.000 for each day or part of a day that this prohibition is wholly or partially breached or - at Grünenthal's discretion - of € 2,5000 for each infringing product with which this prohibition is wholly or partially breached, subject to a maximum of € 1,000,000;

5.2. orders Teva B.V. and Teva Nederland B.V. jointly and severally to pay Grünenthal's legal costs, estimated to date at €40,000;

5.3. sets the time limit for making a claim in the main action as referred to in Section 1019i Rv to six months from today;

5.4. declares this judgment to be provisionally enforceable to this extent;

5.5. Dismisses the more or otherwise claimed.

This judgment was rendered by Mr M.E. Kokke and publicly pronounced on 3 October 2023.