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Datasheet for the decision of 14 February 2019

Case Number: T 0062/16 - 3.3.07

Application Number: 09012462.9

Publication Number: 2158900

IPC: A61K9/00, A61K38/09, A61K47/34

Language of the proceedings: EN

Title of invention:
Polymeric delivery formulations of leuprolide with improved efficacy

Patent Proprietor:
Tolmar Therapeutics, Inc.

Opponent:
Generics (U.K.) Limited (trading as Mylan)

Headword:
Leuprolide/ TOLMAR

Relevant legal provisions:
EPC Art. 99(1), 56
RPBA Art. 13(3)

Keyword:
Admissibility of opposition - (yes)
Inventive step - main and auxiliary requests (no)

Decisions cited:
T 1714/12

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Case Number: T 0062/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 14 February 2019

Appellant: (Opponent)	Generics (U.K.) Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Tolmar Therapeutics, Inc. 701 Centre Avenue Fort Collins, CO 80526 (US)
Representative:	Leifert & Steffan Patentanwälte PartG mbB Patentanwälte Burgplatz 21-22 40213 Düsseldorf (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 13 November 2015 concerning maintenance of the European Patent No. 2158900 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	A. Usuelli
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 2 158 900 was opposed on the grounds that its subject-matter lacked novelty and inventive step, was insufficiently disclosed, and extended beyond the content of the parent application. The following documents were among those cited during the first-instance proceedings:

D1: International Journal of Pharmaceutics 194 January 2000, 181-191
D2: Journal of Pharmaceutical Sciences, 89, 6, June 2000, 732-741
D4: AAPS PharmSciTech, 1(1), article 1, February 2000
D5: Pharmaceutical Research, 8, 6, 1991, 787-791
D11: Physician's Desk Reference, 53rd edition, 1999
D18: Declaration of Dr Bezwada
Annex 3: Printout from internet site of Companies House

II. The opposition division held that the patent and the invention to which it related according to the main request filed on 9 April 2015 met the requirements of the EPC.

This decision was appealed by the opponent (hereinafter "the appellant").

III. Claim 1 of the request considered by the opposition division to comply with the requirements of the EPC, read as follows:

"1. A flowable composition, which is suitable for use as a controlled release implant, for use in the treatment or prevention of prostate cancer in a human, wherein the flowable composition comprises:

(a) a biodegradable thermoplastic polyester being a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof or a combination thereof, the polyester being at least substantially insoluble in aqueous medium or body fluid;
(b) a biocompatible polar aprotic solvent being N-methyl-2-pyrrolidone, 2-pyrrolidone, N,N-dimethylformamide, propylene carbonate, caprolactam, triacetin, or any combination thereof, wherein the biocompatible polar aprotic solvent is miscible to dispersible in aqueous medium or body fluid; and
(c) leuprolide acetate in an amount sufficient to lower LHRH levels in a human."

IV. The opposition division held that the opponent was identifiable beyond doubt on the basis of the information given in the notice of opposition. Thus, contrary to the position of the patent proprietor, the opposition was admissible.

As to inventive step of the main request, the opposition division considered that the injectable microspheres comprising leuprolide acetate mentioned in D1 were the closest prior art. Lupron® was an example of a commercial product based on such injectable microspheres. On the basis of the results disclosed in example 5 of the patent, the technical problem was to be seen in the provision of an improved composition for treating prostate cancer in humans. D1 did not suggest to solve this problem by the provision of the composition defined in claim 1. Hence, the main request met the requirements of Article 56 EPC.

V. The appellant submitted the statement setting out the grounds of appeal on 23 March 2016.

In the reply filed on 7 October 2016, the patent proprietor (hereinafter "the respondent") defended its case on the basis of the request maintained by the opposition division (main request) and on the basis of 11 auxiliary requests numbered 1 to 3, 3a, 4 to 8, 8a and 9, wherein auxiliary requests 3a and 8a were filed with the reply and the remaining requests had already been submitted during the first-instance proceedings on 9 April 2015.

The following documents were annexed to the respondent's reply:

D28: Eur. J. Nucl. Med. Mol. Imaging 2012, 39, 1492-1496
D29: AAPS Journal 2012, 14, 559-570

VI. In a communication pursuant to Article 15(1) RPBA issued on 18 December 2018, the Board commented on inventive step, agreeing with the appellant in considering the Atrigel® formulation disclosed in D1 as a suitable starting point for the assessment of inventive step. It concluded that a skilled person would have been encouraged by the teaching of D1 to start a clinical assessment of the efficacy of the Atrigel® formulation.

VII. By letter of 14 January 2019, the respondent replaced auxiliary requests 5 to 8, 8a and 9 on file with seven new sets of claims named auxiliary requests 5 to 11.

VIII. Claim 1 of auxiliary request 1 differed from claim 1 of the main request (i.e. the request allowed by the opposition division; see point III above) in the indication that the biodegradable thermoplastic polymer

had a molecular weight of 23000 to 45000 or 15000 to 24000.

Claim 1 of auxiliary request 2 differed from claim 1 of the main request in the indication that leuprolide acetate was in an amount of 2 to 4 wt% or 4 to 8 wt% of the composition.

Claim 1 of auxiliary request 3 was based on the combination of the amendments introduced in claim 1 of each of auxiliary requests 1 and 2.

Claim 1 of auxiliary request 3a differed from claim 1 of auxiliary request 3 in specifying that the composition was "formulated as an injectable subcutaneous delivery system".

Claim 1 of auxiliary request 4 differed from claim 1 of auxiliary request 3a in specifying that the composition was "for administration about once per three months or about once per four months to about once per six months".

Claim 1 of each of auxiliary requests 5 to 10 was identical to claim 1 of the main request and each of auxiliary requests 1 to 3, 3a and 4, respectively.

Claim 1 of auxiliary request 11 differed from claim 1 of the main request in specifying that the biodegradable thermoplastic polymer had a molecular weight of 23000 to 45000.

IX. Oral proceedings were held on 14 February 2019.

X. The arguments of the appellant can be summarised as follows:

(a) Admissibility of the opposition

The opposition division was correct in concluding that the opponent was identifiable beyond doubt on the basis of the information given in the notice of opposition. The opposition was therefore admissible.

(b) Inventive step

Document D1 described a study based on a dog animal model for assessing the effectiveness of Atrigel® in the treatment of prostate cancer. The subject-matter of the main request differed from the disclosure of D1 in that the subjects to be treated were humans. The technical problem was the provision of a new medical application of Atrigel®. The authors of D1 concluded that the formulation appeared promising for development into a clinical product. Hence, the skilled person would have been encouraged to test Atrigel® in humans, thereby arriving at the subject-matter of the opposed patent. Moreover, leuprolide acetate was already used in humans for the treatment of prostate cancer. Hence, the skilled person was already aware of any possible side effects caused by this drug. Animal models were commonly used to test new formulations. In particular, as shown in D5 and D11, they were used to estimate the dose to be administered to humans. Thus, the skilled person had no reason to disregard the teaching of D1, for the sole reason that it was based on animal models. The initial high release from Atrigel® reported in D4 would not have discouraged the skilled person from testing this product. Indeed, in D4 it was affirmed that this effect could be advantageous. The subject-matter of the main request was therefore obvious. The subject-matter of the auxiliary requests did not comply

with the requirements of Article 56 EPC essentially for the same reasons as the main request. The limitation introduced in auxiliary request 11 with regard to the molecular weight did not provide any inventive contribution. Indeed, D1 indicated that polymers with this molecular weight were not different in their efficacy profile from the other polymers tested.

XI. The arguments of the respondent can be summarised as follows:

(a) Admissibility of the opposition

It was not possible to unambiguously identify the opponent on the basis of the notice of opposition. The indication "trading as Mylan" could mean that Mylan was doing business by selling the products of Generic (U.K.) or that the business of Mylan was to file oppositions. Thus, the opposition was not admissible since it was not clear which company had filed it.

(b) Inventive step

D1 referred to two products containing leuprolide acetate, namely the microspheres capsules, such as Lupron®, and the polymer drug delivery system Atrigel®. Only Lupron® was already used in humans. Hence, this product was the best starting point for the assessment of inventive step. In any case, the subject-matter of the main request was inventive also when assessing inventive step starting from the product Atrigel®. The technical problem was to provide the first application of Atrigel® in humans. The conclusion in D1, that Atrigel® was a promising formulation for development into a clinical product, was purely speculative. It was based on a small group of animals. According to D28,

the results of underpowered studies were useless. As explained in D29, results obtained from animal models could not easily be transferred to humans. Furthermore, D4 indicated that Atrigel® gave a high initial release of drug. Hence, testing the Atrigel® formulation in humans would have been risky and unethical. The skilled person would have not considered a try-and-see approach in such a situation. Moreover, the use of the Atrigel® formulation had the advantage of reducing pain and discomfort for the patient. This result was not suggested in the prior art. Thus, the subject-matter of the main request was inventive.

The same arguments applied to the auxiliary requests. Claim 1 of auxiliary request 11 was further restricted by the requirement that the thermoplastic polyester had a molecular weight of 23000 to 45000. The conclusion in D1 as to the possibility of starting a clinical development for the Atrigel® formulation did not relate to a formulation having this molecular weight.

XII. The appellant requested that the decision under appeal be set aside and that the patent be revoked. It further requested not to admit auxiliary requests 5 to 11 into the appeal proceedings.

XIII. The respondent requested that the opposition be rejected as inadmissible, or that the appeal be dismissed. In the alternative, it requested that the patent be maintained on the basis of one of the following 12 auxiliary requests:

- auxiliary requests 1 to 3 filed on 9 April 2015
- auxiliary request 3a filed on 7 October 2016 with the reply to the appeal
- auxiliary request 4 filed on 9 April 2015

- auxiliary requests 5 to 11 on 14 January 2019.

Reasons for the Decision

1. Admissibility of the opposition

1.1 The respondent's objection against the admissibility of the opposition is based on the argument that the identity of the opponent could not be established. This is because the name "Generics [UK] Limited (trading as Mylan)" used in the Form 2300E (notice of opposition) leaves doubt as to whether the opposition had been filed by "Generics [UK] Limited" or "Mylan".

1.2 According to Article 99(1) EPC, any person is entitled to file an opposition. Its identity must be sufficiently established by the end of the opposition period.

Annex 3, an extract from the United Kingdom's register of companies, indicates that "Generics (U.K.) Limited" is a registered UK company. Thus, it is a legal person and as such may file an opposition. The fact that in Form 2300E the wording "[UK]" instead of "(U.K.)" is used is a minor error that does not introduce any ambiguity as to the opponent's identity.

1.3 As explained in the respondent's letter of 20 July 2015, the expression "trading as Mylan" indicates that the company is trading under a business name that is not its legal name. In the Board's view, this does not generate any confusion as to the identity of the opponent. The expression "trading as" is not an indication that a company is delegating a third entity to act on its behalf. It merely means that a company

operates under a name different from its registered name.

1.4 The respondent argued that "Mylan's" business could be to file oppositions for "Generics (U.K.) Limited". This rendered unclear which company is filing the opposition.

This argument is not convincing. It follows from the above considerations that the trading name is merely a pseudonym that a company may use in certain circumstances. Moreover, in the present case, the opponent did not use its trading name to file the opposition. In this regard, the information in Form 2300E is clear: it indicates that the opponent is the company "Generics [U.K.] Limited". The name "Mylan" is only mentioned in brackets to indicate that "Generics [U.K.] Limited" is doing business under this name.

1.5 On this basis, the Board agrees with the opposition division's conclusion that it was possible to establish the opponent's identity on the basis of the information given in the notice of opposition. Thus, the opposition of the appellant is admissible.

Main request

2. Inventive step

2.1 The invention underlying the main request concerns a flowable polymeric composition that is injectable and forms an implant *in situ* delivering leuprolide acetate in a controlled manner. The composition is useful in the treatment and prevention of prostate cancer.

2.2 Closest prior art

2.2.1 The parties agree that document D1 is the closest prior art. It is disputed, however, whether the starting point for the assessment of inventive step should be the injectable microspheres mentioned on page 194 (respondent's position) or the Atrigel® product which is tested in the experimental study described in document D1 (appellant's position).

2.2.2 Both the injectable microspheres and the Atrigel® based product contain leuprolide acetate as active ingredient, i.e. a substance that is known to be used in the treatment of hormone dependent prostate carcinoma (see introduction of D1).

The injectable microspheres are simply mentioned on page 194 of D1. The commercial product Lupron® depot, described in D11, is a product available on the market containing leuprolide acetate in microspheres. The product is used in the treatment of advanced prostatic cancer in human. The formulation of the injectable microspheres (including Lupron® depot) is different from the formulation defined in claim 1 of the main request in that it does not contain a solvent.

The Atrigel® based product tested in D1 is identical to the product of claim 1 of the main request. However, in the study described in D1 it has not been used in humans.

2.2.3 Both the Lupron® depot and the Atrigel® based formulation are products conceived for the treatment of prostate cancer. They are therefore suitable starting points for the assessment of inventive step.

According to the established case law of the boards of appeal, if the skilled person has a choice of several workable routes which may lead to the invention, the rationale of the problem-solution approach requires that the invention be assessed relative to all these possible routes, before an inventive step can be acknowledged (see e.g. T 1742/12, point 6 of the Reasons).

In the following sections, the Board will assess inventive step starting from the product Atrigel® as the closest prior art.

2.2.4 The studies disclosed in D1 concern the evaluation of the Atrigel® formulation in rats and dogs. There is no indication in D1 that the animals used in the studies suffer from prostate cancer. Thus, the subject-matter of claim 1 differs from the disclosure of D1 in the use of the composition in the treatment or prevention of prostate cancer in humans. Moreover, D1 does not indicate whether leuprolide acetate is present in an amount sufficient to lower LHRH levels in humans, as required by claim 1.

2.3 Technical problem

2.3.1 The technical problem underlying the invention over D1 can be seen in the provision of a new medical application of Atrigel®.

Example 5 of the patent shows that the subcutaneous injection of the composition of claim 1 into prostate cancer patients results in a progressive reduction of the serum testosterone levels. After 21 days, the testosterone concentration is below the castrate value of 0.5 ng/mL. As explained in paragraph [0001] of the

patent, achieving a circulating testosterone level of less than 0.5 ng/mL is a desired pharmacological indicator of therapeutic action in the treatment of prostate cancer.

Thus, having regard to the experimental results disclosed in the patent, it is credible that the technical problem defined above has been solved by the subject-matter of claim 1.

2.4 Obviousness

2.4.1 The use of leuprolide acetate formulations in the treatment of prostate cancer in humans was already known before the priority date of the patent-in-suit. This is evident, for instance, from the introduction of D1, which indicates that leuprolide solutions for subcutaneous injection are useful in the palliative treatment of hormone dependent prostate cancer. Furthermore, the microsphere-based product Lupron® depot, was available on the market (see abstracts of D4 and D11, page 3145). It was known, furthermore, that reducing the serum testosterone level is an indicator of efficacy of a product in the treatment of prostate cancer (see introduction of D2).

These considerations suggest that, although the objective of the study disclosed in D1 was to observe a biochemical parameter, namely the reduction of serum testosterone in rats and dogs after injection of the Atrigel® formulation, it is clear that this was made in the context of finding a suitable product for the treatment of prostate cancer.

It follows from the above that the indication in claim 1 of the therapeutic indication, namely "prostate

cancer", as such does not provide any inventive contribution to the subject-matter of the claim.

2.4.2 The main argument of the respondent to support the presence of an inventive step is that the skilled person would have not considered to test the Atrigel® formulation disclosed in D1 in humans. In this regard, it argued that the skilled person would have a very cautious approach when considering the possibility of testing a product in humans and would avoid a "try-and-see approach".

2.4.3 The Board agrees with the respondent that the skilled person assessing the possibility of starting a clinical study with a product that has never been tested in humans would have a conservative attitude. Accordingly, they would very likely avoid testing a product that already did not provide very good results in animals trials. The skilled person will also be concerned by issues relating to the safety of the product. They would therefore make a thorough assessment of the possible health risks for the patients before starting a clinical trial.

Therefore, whether or not the skilled person would decide to to start a clinical study with a product that has never been tested in humans is a matter that has to be decided on the basis of the specific circumstance of each case.

2.4.4 In the present case, the product in question, i.e. the Atrigel® formulation containing leuprolide acetate, is presented in D1 as a promising product for treating prostate cancer in humans. Indeed, as underlined in the abstract, Atrigel® reduces the testosterone levels in dogs to the targeted levels of 0.5 ng/ml by day 14 and

up to day 91. Similar results are observed in rats. In the "Conclusions" (page 190), the authors of D1 explicitly state that Atrigel® "appears promising for development into a clinical product".

2.4.5 The Board concurs with the respondent that the results obtained in animal models are not always transferable to humans. Thus, the positive conclusions drawn by the authors of D1 would not be regarded by the skilled person as an absolute guarantee that the same results would be obtained in humans.

This is however a consideration of general validity. During the development of a new pharmaceutical product for use in humans, there will always be the necessity, at some point, to make the step from experimentation with animal models to experimentation with humans. This step will necessarily involve some degree of uncertainty as to the possibility of obtaining the expected results in humans.

Yet, in the present case, this normal uncertainty will not result in a sceptical attitude. The statement in D1, that the formulation tested in rats and dogs appears promising for development into a clinical product, is an indication of the confidence of the authors on the animal models used as tools for predicting the behaviour of the formulation in humans. In this regard, it is also to be considered that the active ingredient, leuprolide acetate, was already used before the priority date in the treatment of prostate cancer in humans (see point 2.4.1 above). Thus, the main objective of a possible clinical study on a new formulation of leuprolide acetate would not be to make observations on the clinical efficacy and safety of the active ingredient, these aspects being well known when

an active ingredient has already received a marketing authorisation. Rather, in such a situation, an important objective of a possible clinical trial would be to determine the suitable dosage for use in humans. In respect of this objective, a study based on animal models already provides important information. For instance, D5 (page 787, first sentence of left-hand column) explains that the human dose of leuprolide acetate for the injectable microsphere was estimated on the basis of the pharmacokinetic parameters determined in rats and dogs. D11 (page 3142, right-hand column) suggests that rats are used for determining overdosage.

The respondent also emphasised that in the study of D1 the Atrigel® formulation was administered only to five dogs. Although this observation is correct, in the Board's, view this issue is also to be considered in relation to the fact that leuprolide acetate was a well-known product already used in humans. Furthermore, as explained in point 7 of D18, sustained release products using absorbable polymers were also commercially available. Thus, having regard to the knowledge already existing with regard to the active ingredient and the type of formulation, the skilled person would have not considered the small number of animal tested as an important limitation of the study of D1. After all, it has to be assumed that when the authors of D1 concluded that the Atrigel® formulation was suitable for a clinical development, they were aware of the number of animals used in the test.

Thus, despite the usual reservations as to the reliability of results obtained from animal models, in the Board's view, the skilled person would have had no reason to disregard the teaching of document D1; quite the contrary, the conclusion drawn in this document

would have encouraged the skilled person to start clinical tests with Atrigel®.

2.4.6 The fact that leuprolide acetate was already used in humans also plays an important role when assessing the possible health risks for the patients to be enrolled in a possible clinical study of a formulation containing that drug. Indeed, in such a situation, not only the therapeutic properties of the active ingredient are known but also the potential side effects associated with its use, the cases in which its use is contraindicated, the precautions to taken before its administration and the consequences of an overdosage. Additionally, it follows from the declaration of Dr Bezwada (D18, point 7) that a number of commercial sustained release products using absorbable polymers of the same type of those defined in claim 1 of the main request were available in the marketplace. Hence, it can be assumed that the skilled person could retrieve information also with regard to adverse reactions caused by the excipients of the formulation.

Accordingly, the skilled person evaluating the possibility of testing the Atrigel® formulation of D1 on humans was in a position to make a realistic assessment of the potential risks for the health of the persons to be enrolled in such test.

Hence, in relation to the health risks, the Board is in unable to see any specific reason that would have led the skilled person to disregard the clear conclusion reached by the authors of D1 as to the fact that Atrigel® is a promising candidate for development into a clinical product. Furthermore, apart from the considerations concerning the health risks, no specific

argument has been submitted by the respondent regarding any possible ethical issue.

2.4.7 Referring to Figure 4 of D4, the respondent observed that the administration of Atrigel® in dogs gives a high initial release of active ingredient. This would have discouraged the skilled person from using this product in humans. The Board does not agree with this conclusion because on page 7 of D4 it is affirmed that the inherent property of initial high release can be termed advantageous or disadvantageous only on a case-specific basis. Thus, this feature of the Atrigel® formulation is not presented in D4 as a drawback of the product. Indeed, in the conclusion of D4, the Atrigel® formulation is described in positive terms as a product suitable for obtaining and maintaining suppressed testosterone levels from day 14 to 91. Consistently with D1, D4 states that the formulation is a candidate for further development.

As a further argument, the respondent explained that the use of the Atrigel® formulation facilitated a painless administration of leuprolide acetate. However, this property of the formulation is also recognised in the conclusions of D1. Thus, this advantageous effect does not support the presence of an inventive step.

2.4.8 As discussed in point 2.2.4 above, D1 does not indicate whether Atrigel® contains leuprolide acetate in an amount sufficient to lower LHRH levels in humans, as required by claim 1. The respondent did not submit any specific argument as to the relevance of this feature in the assessment of inventive step. The Board notes that there is no indication in the patent that invention lies in the discovery that leuprolide acetate lowers LHRH.

Moreover, the indication "in an amount sufficient to lower LHRH" is a functional definition of the amount of active ingredient in the formulation. Dependent claim 7 specifies that this amount is between 4 wt% to 8 wt% of the composition. Table 1 of D1 describes Atrigel® formulations comprising 4.5 wt% and 6 wt% drug load (formulations G and H). Hence, the functional definition used in claim 1 to define the amount of leuprolide acetate covers formulations disclosed in D1. Thus, this functional definition does not provide any inventive contribution to the subject-matter of claim 1.

2.4.9 On the basis of the above considerations, the Board concludes that the subject-matter of claim 1 does not involve an inventive step.

In view of this conclusion, it is not necessary to consider the alternative approach to the question of inventive step starting from the product Lupron® as the closest prior art.

Auxiliary request 1

3. Claim 1 of auxiliary request 1 specifies that the biodegradable thermoplastic polymer has a molecular weight of 23000 to 45000 or 15000 to 24000.

3.1 Table 1 in D1 discloses Atrigel® formulations in which the biodegradable polymer has a molecular weight included in the range 23000 to 45000 (formulation E) or in the range 15000 to 24000 (e.g. formulations A to D). Hence, the limiting feature introduced in auxiliary request 1 does not provide any contribution over the teaching of D1. Thus, this request does not comply with

Article 56 EPC for the same reasons as the main request.

Auxiliary request 2

4. Claim 1 of this request differs from claim 1 of the main request in the indication that leuprolide acetate is in an amount of 2 to 4 wt% or 4 to 8 wt% of the composition.

4.1 All the Atrigel® formulations disclosed in Table 1 of D1 have a drug load included in the ranges defined in auxiliary request 2. Hence, auxiliary request 2 also does not comply with the requirements of Article 56 EPC.

Auxiliary request 3

5. Claim 1 of auxiliary request 3 is based on the combination of the amendments introduced in claim 1 of auxiliary requests 1 and 2. Hence, this request is not inventive for the same reasons as the previous auxiliary requests.

Auxiliary request 3a

6. Claim 1 of auxiliary request 3a differs from claim 1 of auxiliary request 3 in specifying that the composition is "formulated as an injectable subcutaneous delivery system"

6.1 In the experiments disclosed in D1, the Atrigel® formulations are administered to rats and dogs by subcutaneous injection (paragraphs 2.2.4.1 and 2.2.4.2). Thus, the feature introduced in claim 1 of auxiliary request 3a does not provide any inventive

contribution over D1. Hence, this request also does not comply with Article 56 EPC.

Auxiliary request 4

7. Claim 1 of this request specifies that the composition is formulated as an injectable subcutaneous delivery system for administration about once per three months or about once per four months to about once per six months.

7.1 As discussed in point 2.4.4, D1 reports that the leuprolide acetate Atrigel® formulation reduces the testosterone levels in dogs to less than 0.5 ng/mL by day 14 and up to day 91. This is a pharmacological indicator of therapeutic action in the treatment of prostate cancer.

On the basis of this information, the skilled person would have considered it obvious to administer the leuprolide acetate Atrigel® formulation about once per three months. Hence, auxiliary request 4 is also not inventive.

Admissibility of auxiliary requests 5 to 11

8. These requests were filed on 14 January 2019, i.e. one month before the oral proceedings.

Auxiliary requests 5 to 10 are based on the main request and auxiliary requests 1 to 3, 3a and 4 respectively. They differ from these requests only in the deletion of dependent claims 6 and 8. Claim 1 of auxiliary request 11 differs from claim 1 of auxiliary request 1 in that the biodegradable polymer has been limited to the polymers having a molecular weight of

23000 to 45000 (i.e. deletion of the feature "or 15000 to 24000"). Further, dependent claims 6 and 8 of auxiliary request 1 have been excluded from auxiliary request 11.

8.1 It follows from the above, that auxiliary requests 5 to 11 relate to subject-matter which is incorporated in the main request or in auxiliary requests 1 to 3, 3a and 4, i.e. in requests that have always been part of the appeal proceedings.

Hence, the filing of auxiliary requests 5 to 11 does not raise any issues which the Board or the appellant cannot be reasonably expected to deal with without adjournment of the oral proceedings (Article 13(3) RPBA).

Accordingly, these requests are admitted into the appeal proceedings.

Auxiliary requests 5 to 10 - Inventive step

9. Claim 1 of each of auxiliary requests 5 to 10 is identical to claim 1 of the main request and each of auxiliary requests 1 to 3, 3a and 4, respectively. Accordingly, these requests also do not comply with the requirements of Article 56 EPC.

Auxiliary request 11 - Inventive step

10. Claim 1 of auxiliary request 11 specifies that the biodegradable thermoplastic polymer has a molecular weight of 23000 to 45000.

In the respondent's opinion, the conclusion in D1 as to the possibility of starting a clinical development for

the Atrigel® formulation relates to a formulation wherein the polymer has a molecular weight around 15000, i.e. outside of the range 23000 to 45000 of auxiliary request 11. For this reason, the subject-matter of this request would not be obvious over the teaching of D1.

10.1 The Board notes that the leuprolide acetate Atrigel® formulations tested in the experiments of D1 include formulation E, which comprises a biodegradable polymer having a molecular weight of 26762, i.e. included in the range of claim 1 of auxiliary request 11 (see Table 1). The effects of the molecular weight of the polymer in suppressing serum testosterone levels are discussed in D1 starting from page 188. It is stated that polymers B and E were not significantly different in their efficacy profile. Polymer B has a molecular weight of 15705 (see Table 1). Thus, D1 indicates that a polymer having a molecular weight around 26000 has substantially the same efficacy as a polymer of a molecular weight around 15000. Indeed, on page 189 it is stated that formulations containing a 75/25 poly (DL-lactide-co-glycolide) polymer with a molecular weight in the range 15600 to 27000 could provide efficacious formulations. Only polymers with a molecular weight of approximately 6000 or less would not be suitable for 90-day release of the drug.

It follows that a skilled person would regard any Atrigel® formulation comprising a polymer with a molecular weight in the range 23000 to 45000 as being substantially equivalent, in terms of efficacy in lowering the testosterone levels, as a formulation comprising a polymer with a molecular weight of around 15000. Hence, they would also consider that formulations made from polymers with a molecular weight

in the range 23000 to 45000 are suitable candidates for development into clinical products.

Thus, auxiliary request 11 is not inventive either.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos J. Riolo

Decision electronically authenticated