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Datasheet for the decision of 9 September 2019

Case Number: T 0548/15 - 3.3.01

Application Number: 10175858.9

Publication Number: 2292225

IPC: A61K31/335, A61L31/16, A61P7/00, A61F2/06, A61K31/16

Language of the proceedings: EN

Title of invention:
Dosage form comprising taxol in crystalline form

Patent Proprietor:
BOSTON SCIENTIFIC SCIMED LIMITED

Opponent:
Terumo Kabushiki Kaisha

Headword:
Crystalline taxol/BOSTON

Relevant legal provisions:
EPC Art. 100(b), 83, 56

Keyword:
Sufficiency of disclosure - main request and auxiliary requests 1 to 7 (no)
Inventive step - auxiliary request 8 (no)

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Case Number: T 0548/15 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 9 September 2019

Appellant: (Opponent)	Terumo Kabushiki Kaisha 44-1, Hatagaya 2-Chome Shibuya-ku Tokyo 151-0072 (JP)
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Respondent: (Patent Proprietor)	BOSTON SCIENTIFIC SCIMED LIMITED The Corporate Centre Bush Hill, Bay Street St. Michael (BB)
Representative:	Peterreins Schley Patent- und Rechtsanwälte Hermann-Sack-Strasse 3 80331 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 January 2015 rejecting the opposition filed against European patent No. 2292225 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	L. Bühler

Summary of Facts and Submissions

I. The present appeal lies from the decision of the opposition division pronounced at the oral proceedings on 12 December 2014 rejecting the opposition filed against European patent No. 2292225.

Claim 1 as granted read as follows:

"*1. A dosage form comprising a taxol for use in inhibiting or reducing diminution in vessel lumen area of a mammalian blood vessel, wherein the taxol is in substantially crystalline form and wherein the crystal size of the taxol is 0.1 micron to 1 mm.*"

II. The following documents, cited during the opposition/ appeal proceedings, are referred to below:

D3: WO 95/03795

D17: Study "Paclitaxel Morphology Effects on DEB PK" filed by the respondent on 23 September 2013

D29: J.F. Granada et al., Open Heart, 6 August 2014, 1-11

D30: C.J. Creel, et al., Circulation Research, 86, 2000, 879-884

D36: EP-A-0 473 326

D37: X. Li et al., Protein Cell, 2(3), 2011, 189-201

D37a: H.C. Stary et al., Circulation, 89(5), 1994, 2462-2478

X4: WO 92/11890

III. The patent had been opposed on the grounds of Articles 100(c), 100(b) and 100(a) EPC, for lack of novelty and inventive step.

In the appealed decision, the opposition division concluded that the patent as granted did not add subject-matter and that its invention was sufficiently disclosed, novel and inventive.

IV. With the statement of grounds of appeal, the opponent (appellant) filed new documents and argued why, in its opinion, the decision under appeal should be set aside and the patent be revoked.

In subsequent letters, the appellant filed *inter alia* document D36 (letter dated 11 January 2018).

V. With its reply to the statement of grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed. Alternatively, it requested that the patent be maintained on the basis of any of the claim sets filed on 11 November 2014 as auxiliary requests 1 to 7 or on the basis of the auxiliary request 8 filed with the reply to the statement of grounds of appeal.

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it specifies that the crystals are of a size which results in sustained release of taxol.

Claim 1 of auxiliary request 2 is based on claim 1 of auxiliary request 1, with the additional limitation that the crystal size of taxol is 1 micron to 1 mm.

Claim 1 of auxiliary request 3 is identical to claim 1 of auxiliary request 2.

Claim 1 of each of auxiliary requests 4 and 5 are based on claim 1 of each of auxiliary requests 1 and 2 respectively, with the additional limitation that taxol is administered via an implantable device.

Claim 1 of auxiliary request 6 is based on claim 1 of auxiliary request 5, with the additional limitation that the device is an adventitial wrap, an artificial graft, a catheter, a stent or a shunt.

Claim 1 of auxiliary request 7 is based on claim 1 of auxiliary request 2, with the additional limitation that the dosage form is delivered locally by a catheter which is introduced into the afflicted vessel during the procedure.

Claim 1 of auxiliary request 8 is based on claim 1 as granted, wherein the diminution of vessel lumen area has been specified to be restenosis.

VI. A third party filed observations on 11 August 2016 and 24 August 2017.

VII. In a communication dated 4 June 2019, the board gave its preliminary opinion. It noted *inter alia* that, according to the patent (see paragraph [0020]), the term taxol encompasses taxol analogues, equivalents and derivatives such as the water-soluble taxol derivatives disclosed in document D36. However, water-soluble derivatives would not provide sustained release of taxol. The board also drew attention to the fact that the invention would not be sufficiently disclosed if

the diminution in vessel lumen area were caused by a factor other than smooth muscle cell proliferation.

VIII. In response to the board's preliminary opinion, the respondent announced that it would not attend the oral proceedings and the appellant filed several documents, including documents D37 and D37a.

IX. Oral proceedings were held before the board on 9 September 2019 in the absence of the respondent.

X. The appellant's arguments, where relevant to the present decision, may be summarised as follows:

The invention of claim 1 of each of the main request and auxiliary requests 1 to 7 is not sufficiently disclosed because the claimed therapeutic effect is not achieved across the whole breadth of the claims. The claims are directed to the use of taxol for reducing or preventing a diminution in vessel lumen area irrespective of its origin. However, although taxol may be suitable to treat a diminution in vessel lumen area caused by smooth muscle cell proliferation, it is ineffective when the diminution in vessel lumen area is caused by other factors such as dyslipidemia (see documents D37 and D37a).

The subject-matter of claim 1 of auxiliary request 8 is not inventive. Document D3, which concerns the use of taxol for the prevention or reduction of restenosis, is the closest prior art. The subject-matter of claim 1 differs from it in that taxol is administered in crystalline form having a crystal size of 0.1 micron to 1 mm. Contrary to the respondent's view, document D17 does not demonstrate that this difference results in an improved effect. Hence, the objective technical problem

is the provision of a suitable form of taxol for local delivery to inhibit or reduce restenosis. The solution proposed in claim 1 was obvious in view of document X4, which suggests the treatment of stenosis and the prevention of restenosis by the local administration to a blood vessel wall through a drug-eluting balloon catheter of a crystalline drug which controls smooth muscle cell proliferation. In particular, document X4 suggests the provision of crystals encapsulated into microcapsules of 2 to 100 microns.

XI. The respondent's arguments, where relevant to the present decision, may be summarised as follows:

Document D3 is the closest prior art. The subject-matter of claim 1 of auxiliary request 8 differs from it in that taxol is in substantially crystalline form with a crystal size of 0.1 micron to 1 mm. Document D17 shows that crystalline taxol is superior to amorphous taxol in that the amount of taxol locally delivered to blood vessel tissues is substantially higher. This effect is confirmed by the results presented in documents D29 and D30 and produces an increased therapeutic effect of crystalline taxol. The objective technical problem may then be formulated as the provision of a safer taxol dosage form that also has increased therapeutic efficacy. None of the cited prior art documents makes obvious the administration of taxol in crystalline form, let alone having a crystal size of 0.1 micron to 1 mm, to solve the problem posed. In particular, document X4 neither deals with improving the efficacy of the drug administered with the drug-eluting balloon catheter nor mentions taxol. Thus, a consideration of document X4 could only be made with hindsight.

XII. The final requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and that European patent No. 2292225 be revoked.

The respondent requested in writing that the appeal be dismissed and the patent be maintained as granted. Alternatively, it requested that the patent be maintained in amended form on the basis of any of the claim sets filed on 11 November 2014 as auxiliary requests 1 to 7 or the claim set filed with the reply to the statement of grounds of appeal (12 October 2015) as auxiliary request 8.

XIII. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

1. The oral proceedings before the board took place in the absence of the respondent, who was duly summoned but chose not to attend, as announced with the letter of 9 July 2019.

In accordance with Rule 115(2) EPC, the board decided to continue the proceedings in the respondent's absence. Pursuant to Article 15(3) RPBA, the board was not obliged to delay any step in the proceedings, including its decision, by reason only of the respondent's absence at the oral proceedings. In line with this provision, the respondent was treated as relying on its written case. Hence, the board was in a

position to announce a decision at the conclusion of the oral proceedings, in accordance with Article 15(6) RPBA.

2. Sufficiency of disclosure - claim 1 as granted

2.1 The invention underlying claim 1 as granted is based on the ability of taxol to inhibit the proliferation of smooth muscle cells in the intimal layers of a mammalian blood vessel, thereby preventing a reduction of the vessel lumen area (see e.g. paragraph [0005] and examples in the patent). This proliferation of smooth muscles cells occurs typically when the vessel is traumatised, e.g. following vascular surgery.

2.2 Comparing the wording of claim 1 with the way the invention works, the question that arises is whether there is always an overgrowth of smooth muscle cells at the origin of a diminution in mammalian vessel lumen area. If this were not the case, the suitability of taxol to reduce any diminution in vessel lumen area would be questionable.

This question was posed by the board in its preliminary opinion dated 4 June 2019 (point 6). In response to it, the appellant filed *inter alia* documents D37 and D37a. The respondent neither filed submissions nor objected to the admission of documents D37 and D37a.

2.3 The board holds that the filing of documents D37 and D37a constituted an adequate response to the board's preliminary opinion and that both documents are highly relevant because they explain how blood vessel lumen area is reduced and which cell types are involved at the different stages of atherosclerosis. Hence, the

board admitted both documents into the proceedings (Article 13 RPBA).

2.4 According to documents D37 and D37a (see D37, page 189, right-hand column and figure 1; and D37a, abstract and headline on page 2472, "Macrophages and Macrophage Foam Cells"), at earlier stages of atherosclerosis, high plasma concentrations of low-density lipoprotein (LDL) cause the infiltration of LDL into the arterial wall. Subsequently, the oxidation of the retained LDL stimulates the adhesion of monocytes which migrate to the sub-endothelial space of the vessel, differentiate into macrophages, and take up the oxidised LDL developing into lipid-rich foam cells. The accumulation of foam cells within the vessel wall reduces the vessel lumen area. Smooth muscle cells are first involved at later, intermediate stages, at which they migrate from the media layer into the intimal or sub-endothelial space of the vessel and proliferate.

This mechanism of atherosclerosis reveals that, at earlier stages, the reduction of blood vessel lumen area is not caused by a proliferation of smooth muscle cells but by the accumulation of LDL and macrophages into the vessel sub-endothelial space. Hence, at those stages taxol cannot inhibit or reduce a diminution in the vessel lumen area and the effect defined in claim 1 is not achieved.

Considering that the reduction or inhibition of the diminution in vessel lumen area is a functional feature of claim 1 and that it cannot be achieved across its whole breadth, the invention of claim 1 lacks sufficiency of disclosure (Article 83 EPC).

3. Sufficiency of disclosure - auxiliary requests 1 to 7

Claim 1 of each of auxiliary requests 1 to 7 contain restrictions with regard to the form in which taxol is administered but not with regard to the factor which diminishes the vessel lumen area; the invention still relies on taxol for inhibiting or reducing a diminution in vessel lumen area of a mammalian blood vessel in general. However, as taxol is not suitable to inhibit or reduce a diminution in vessel lumen area when this is caused by a factor other than an overgrowth of smooth muscle cells (see section 2.4 above), the invention of claim 1 of each of auxiliary request 1 to 7 lacks sufficiency too (Article 83 EPC).

4. Inventive step - auxiliary request 8

4.1 Claim 1 of auxiliary request 8 is directed to the use of crystalline taxol with a crystal size of 0.1 micron to 1 mm for inhibiting or reducing restenosis of a mammalian blood vessel. This crystalline form of taxol allows its local administration over extended periods of time to prevent restenosis resulting from an overgrowth of smooth muscle cells (see patent, paragraphs [0004], [0005] and [0009]).

4.2 It was common ground between the parties that document D3 represents the closest prior art. This document illustrates the effectiveness of taxol or water soluble taxol derivatives in inhibiting the proliferation and migration of vascular smooth muscle cells *in vitro* and in rats (see page 11, lines 16-21 and examples), and claims their use for preventing or reducing restenosis after arterial injury (see claims 1, 2 and 7-9; abstract; page 7, lines 5-19; and page 9, lines 26-30).

Regarding the mode of administration, document D3 proposes several alternatives, including the local delivery (see page 8, lines 5-9). In particular, D3 suggests (see page 10, lines 25-29) the local administration of taxol as a sustained-release preparation because this provides a high dosage local drug delivery with little systemic toxicity. This idea is further reinforced on page 20, lines 4-8, where the document states:

"*Ultimately, local sustained-release delivery systems may offer the best solution to prevent restenosis post-angioplastic, enabling high local concentrations of drug delivery and essentially eliminating problems of systemic toxicity.*"

4.3 The subject-matter of claim 1 differs from the closest prior art in that taxol is administered in crystalline form with a crystal size ranging from 0.1 micron to 1 mm. This form of administration provides the local sustained-release of taxol desired in document D3.

In this context, the respondent filed the experimental report D17. This shows the results of the local administration of taxol to the injured coronary arterial wall of animals by means of a drug eluting balloon catheter, and provides a comparison between the average taxol tissue concentration in the vessel wall when taxol is provided in crystalline or in amorphous form. The study concludes that the crystalline form achieves an effective delivery of taxol for up to 45 days, while the amorphous form is rapidly cleared (see table 3.2, figure 3.1, and section 3.3).

Based on these results, the respondent considered that the technical problem solved by the subject-matter of

claim 1 was the provision of a safer taxol dosage form which also has an increased therapeutic efficacy.

The board cannot agree with this formulation of the problem because the study of document D17 is very specific and does not make credible that the taxol crystals defined in claim 1 always result in an improved local delivery of taxol. This results from the fact that, according to the patent (see paragraph [0020]), the term "taxol" includes not only taxol but also its functional analogues, equivalents or derivatives. Thus, taxol in the patent encompasses for instance the water soluble derivatives of taxol disclosed in table 9 of document D36. As those taxol derivatives can be expected to be quickly washed away when deposited on the inner surface of the blood vessel (they are water-soluble), the improved local delivery shown in D17 for taxol crystals compared to amorphous taxol cannot be expected to arise across the whole breadth of claim 1. In consequence, the technical problem has to be defined in a less ambitious manner, namely as the provision of an alternative dosage form of taxol for use in inhibiting or reducing restenosis of a mammalian blood vessel.

4.4 As mentioned above, document D3 suggests the local, sustained administration of high doses of taxol to improve its efficacy and avoid the side effects of systemic administration. Document X4 teaches precisely how to deliver such high doses of a drug locally to the lumen wall of blood vessels, namely by using a balloon angioplasty catheter which bears the drug coated onto its surface (see page 6, lines 16-21). In particular, document X4 mentions (see page 4, lines 15-21) that in order to prevent restenosis in blood vessels, the drug may for instance be adhered to the ballon wall in

crystalline form. As an option, drug crystals may be encapsulated into microcapsules of 2 to 100 microns (see page 5, lines 4-10).

Hence, starting from document D3 and in view of the teaching of document X4, the skilled person wishing to solve the problem posed would have administered taxol crystals of no more than 100 microns to the blood vessel wall as an obvious measure. By doing so, they would have arrived at the subject-matter of claim 1 without the involvement of an inventive step (Article 56 EPC).

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:

M. Schalow A. Lindner

Decision electronically authenticated