

Internal distribution code:

- (A) [-] Publication in OJ
- (B) [-] To Chairmen and Members
- (C) [-] To Chairmen
- (D) [X] No distribution

**Datasheet for the decision
of 15 June 2023**

Case Number: T 0676/21 - 3.3.07

Application Number: 09757601.1

Publication Number: 2313087

IPC: A61K9/48, A61K9/10, A61K47/14,
A61K47/24, A61K47/44,
A61K31/404

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL DOSAGE FORM FOR IMMEDIATE RELEASE OF AN
INDOLINONE DERIVATIVE

Patent Proprietor:
Boehringer Ingelheim International GmbH

Opponents:
Teva Pharmaceutical Industries Ltd.
Generics (U.K.) Limited
Ter Meer Steinmeister & Partner Patentanwälte mbB

Headword:
Pharmaceutical dosage form for immediate release of an
indolinone derivative / BOEHRINGER INGELHEIM

Relevant legal provisions:

RPBA 2020 Art. 13(2)

EPC Art. 123(2), 83, 56

Keyword:

Amendment after summons - exceptional circumstances (yes)

Amendments - allowable (yes)

Sufficiency of disclosure - (yes)

Inventive step - (yes)



Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 0676/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 June 2023

Appellant: Boehringer Ingelheim International GmbH
(Patent Proprietor) Binger Strasse 173
55216 Ingelheim am Rhein (DE)

Representative: Hoffmann Eitle
Patent- und Rechtsanwälte PartmbB
Arabellastraße 30
81925 München (DE)

Appellant: Teva Pharmaceutical Industries Ltd.
(Opponent 1) 124 Dvora HaNevi'a St.
6944020 Tel Aviv (IL)

Representative: Lederer & Keller Patentanwälte
Partnerschaft mbB
Unsöldstraße 2
80538 München (DE)

Appellant: Generics (U.K.) Limited
(Opponent 2) Building 4, Trident Place
Mosquito Way
Hatfield Herts AL10 9UL (GB)

Appellant: Ter Meer Steinmeister & Partner Patentanwälte mbB
(Opponent 3) Nymphenburger Strasse 4
80335 München (DE)

Representative: Ter Meer Steinmeister & Partner
Patentanwälte mbB
Nymphenburger Straße 4
80335 München (DE)

Decision under appeal: Interlocutory decision of the Opposition
Division of the European Patent Office posted on
6 April 2021 concerning maintenance of the
European Patent No. 2313087 in amended form.

Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
L. Basterreix

Summary of Facts and Submissions

- I. European patent 2 313 087 (hereinafter "the patent") was granted on the basis of ten claims. Claim 1 of the patent read as follows:
- "Pharmaceutical dosage form of the active substance 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate, which delivers an immediate release profile in which not less than 70% (Q65%) of the active substance is dissolved in 60 minutes *in vitro* under the following *in vitro* dissolution conditions according to European Pharmacopeia 6.2: Apparatus 2 (paddle), dissolution medium with 0.1 M HCl (pH 1) and stirring speed of 50 to 150 rpm, at a temperature of 37°C and which comprises a viscous lipid suspension formulation comprising 10 to 50 weight% of the active substance, 10 to 70 weight % of medium chain triglycerides, 1 to 30% weight % of hard fat and 0.1 to 10 weight % of lecithin, based on the total weight of the viscous lipid suspension formulation."
- II. In the following, nintedanib esilate refers to the active substance 3-Z-[1-(4-(N-((4-methyl-piperazin-1-yl)-methylcarbonyl)-N-methyl-amino)-anilino)-1-phenyl-methylene]-6-methoxycarbonyl-2-indolinone-monoethanesulphonate. MCT refers to medium chain triglycerides.
- III. Three oppositions were filed against the patent on the grounds that its subject-matter lacked novelty and inventive step, it was not sufficiently disclosed and

it extended beyond the content of the application as filed.

- IV. The opposition division took the interlocutory decision that, on the basis of auxiliary request 1, the patent met the requirements of the EPC.

The decision was based on the patent as granted as the main request, and on auxiliary request 1 filed during the oral proceedings on 12 March 2021.

In claim 1 of this auxiliary request 1, the definition of the viscous lipid suspension formulation was amended to "a viscous lipid suspension formulation of 10 to 50 weight% of the active substance in 1 to 70 weight % of medium chain triglycerides, 1 to 30 weight % of hard fat and 0.1 to 10 weight % of lecithin, based on the total weight of the viscous lipid suspension formulation".

- V. The appealed decision cited the following documents among others:

D2: L. Lachman, "The Theory and Practice of Industrial Pharmacy", 3rd edition, Lea & Febiger, 1986, pages 398-412

D3: W. Fahrig, U. Hofer, "Die Kapsel - Grundlage, Technologie und Biopharmazie einer modernen Arzneiform", Wissenschaftliche Verlagsgesellschaft mbH, 1983, pages 60-63

D4: R. C. Rowe, "Handbook of pharmaceutical excipients", 5th edition, Pharmaceutical Press, 2006, pages 409-411

D6: WO 2004/013099 A1

D7: US 4829057 A

D15: Oral lipid-based formulations, Drugs and pharmaceutical sciences, vol. 170, David J Hauss, 2007, page 88

D16: Protein based films and coatings. Chapter 16: Soft Gelatin Capsules, edited by A. Gennadios, 2002, pages 393-443

VI. The opposition division decided that:

- (a) Claim 1 of the main request introduced added subject-matter.
- (b) Auxiliary request 1 met the requirements of Article 123(2) EPC. Its subject-matter was sufficiently disclosed.

Starting from the closest prior art D6, the subject-matter of claim 1 differed in that it defined a dosage form which comprised a viscous lipid suspension of nintedanib esilate in MCT, hard fat and lecithin, in the amounts claimed, and that the dosage form delivered a specific release profile as claimed. The technical problem was the provision of a pharmaceutical dosage form comprising nintedanib esilate having acceptable bioavailability, low inter-individual variation, and delivering an immediate release as claimed. The claimed solution involved an inventive step.

VII. The patent proprietor and all three opponents lodged appeals against the opposition division's decision.

VIII. With their respective grounds of appeal, opponents 2 and 3 filed D26-D28, and opponent 1 filed D29.

D26: GB395546

D27: US 2,720,463

D28: US 2,870,062

D29: Fiedler Encyclopedia of Excipients, 6th edition, 2007, pages 1326-1327 (filed by appellant 01 as D26)

- IX. The patent proprietor defended their case on the basis of the patent as granted as main request in their grounds of appeal, and additionally filed auxiliary requests 1-4 with their reply dated 2 December 2021. Auxiliary request 1 was identical to auxiliary request 1 as upheld by the opposition division (see IV. above).
- X. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.
- XI. Opponent 3 withdrew their appeal by letter dated 6 April 2023.
- XII. Oral proceedings were held before the Board on 15 June 2023. During the oral proceedings, the patent proprietor withdrew their appeal and filed an amended auxiliary request 1.

In claim 1 of this amended auxiliary request 1, the definition of the viscous lipid suspension formulation was amended to "a viscous lipid suspension formulation of 10 to 50 weight% of the active substance in 10 to 70 weight % of medium chain triglycerides, 1 to 30 weight % of hard fat and 0.1 to 10 weight % of lecithin, based on the total weight of the viscous lipid suspension formulation".

- XIII. The patent proprietor (respondent P) requests that the decision under appeal be set aside and that the patent be maintained on the basis of auxiliary request 1 filed during the oral proceedings on 15 June 2023, or one of

auxiliary requests 2-4 filed with the reply dated 2 December 2021. Respondent P further requests that D29 be not admitted into the proceedings.

XIV. Opponent 1 (appellant O1) and opponent 2 (appellant O2) request that the decision under appeal be set aside and that the patent be revoked in its entirety.

XV. The appellants opponents' arguments may be summarised as follows:

The lipid suspension formulation had been disclosed in the application as filed only in connection with (i.e. as the filler of) soft gelatine capsules, or at least capsules. Auxiliary request 1 thus contained added subject-matter.

To the extent that the *in vitro* dissolution profile was not inherent to the structural features of the claim, namely the choice of formulation components, the criteria of sufficiency of disclosure were not met as regards the achievement of this claimed immediate release profile. The claimed invention could not be performed without undue burden over the whole range claimed.

The closest prior art D6 showed nintedanib esilate formulated in soft gelatine capsules, and implicitly disclosed an immediate release profile. The differentiating feature of claim 1 was the (viscous) lipid suspension formulation of 10-50 wt% of the active substance in 10-70 wt% MCT, 1-30 wt% hard fat and 1-10 wt% lecithin, based on the total weight of the viscous lipid suspension formulation. The technical problem was the provision of an alternative immediate release formulation of nintedanib. The claimed solution,

consisting in the choice of standard excipients, was obvious in light of common general knowledge or alternatively in light of D7 cited in D6.

XVI. Respondent P's arguments may be summarised as follows:

Auxiliary request 1 complied with Article 123(2) EPC. The application as filed described advantages associated with soft gel capsules, but also disclosed the claimed lipid suspension formulation independently of encapsulation.

Regarding sufficiency of disclosure, the appellants-opponents had not provided serious doubts substantiated by verifiable facts that the invention could not be put into practice over the whole scope of the claims.

Starting from D6 as the closest prior art, the claimed subject-matter differed in that the dosage form comprised a viscous lipid suspension of nintedanib esilate in MCT, hard fat and lecithin in the claimed amounts. The dosage form delivered the claimed specific release profile. The technical problem was to provide an improved immediate release formulation of nintedanib having reduced inter-individual variation and acceptable bioavailability and stability. The claimed solution was not obvious in light of the common general knowledge or D7.

Reasons for the Decision

1. Filing and admittance of amended auxiliary request 1

In the course of the oral proceedings in appeal, the Board pointed out for the first time that, according to the then pending auxiliary request 1 (as upheld by the opposition division), the viscous lipid suspension contained **1** to 70% MCT. In contrast, in claim 1 of the granted patent, the viscous lipid suspension contained **10** to 70 w% MCT (see I. and IV. above). This amendment, which had been overlooked by all up to the oral proceedings, obviously contravenes Article 123(3) EPC since the extent of protection is thereby extended to suspensions containing lower amounts of MCT.

Respondent P stated that this was a typographical error and filed, during the oral proceedings before the Board, a new auxiliary request 1 replacing auxiliary request 1 previously on file (see XII. above) and restoring the range 10-70 w% MCT.

The filing of this amended auxiliary request 1 at this stage of the appeal proceedings is occasioned by the above exceptional circumstances, in the sense of Article 13(2) RPBA 2020, and was not objected to by any of the appellants opponents.

This amended auxiliary request 1 was thus admitted by the Board into the proceedings, and constitutes respondent P's highest ranking request. The present decision is based on this amended auxiliary request 1.

2. Article 123(2) EPC

2.1 Claim 1 of auxiliary request 1 relates to a pharmaceutical dosage form of nintedanib esilate delivering an immediate release profile as defined in claim 1, and comprising a viscous lipid suspension formulation of 10-50 wt% of the active substance, in
10-70 wt% of MCT,
1-30 wt% of hard fat and
0.1-10 wt% of lecithin,
based on the total weight of the viscous lipid suspension formulation.

2.2 Appellant O1 contends that a lipid suspension formulation is only disclosed in the application as filed, and can only be considered, in the context of soft gelatine capsules, or at least in the context of capsules. The omission of this limitation in claim 1 of auxiliary request 1 would infringe Article 123(2) EPC.

The Board does not share this view.

The application as filed (see the paragraph bridging pages 17-18) discloses a viscous liquid suspension formulation of nintedanib esilate in a lipid carrier, a thickener and a glidant/solubilizing agent. The types and amounts of the components are shown in subsequent passages on pages 18-20 (see the appealed decision, §14.2). Contrary to appellant O1's opinion, there is no reason to consider that the mention on said page 17 of "The above-mentioned lipid suspension formulation" refers to the suspension encapsulated in a soft gelatine capsule mentioned on page 16, line 21. The lipid suspension formulation is an embodiment of the suspensions generally described on page 15 without limitation to any encapsulation.

Furthermore, the application as filed on page 22 (lines 13-19) indicates that the liquid suspension formulation "may be part", and thus is not necessarily part, of a capsule dosage form.

Lastly, a liquid suspension may be administered by any known means, including in liquid form. An encapsulation of the liquid suspension is technically not necessary, and is merely described as a very convenient way of administration (see page 14, lines 14-22). Likewise, the mentioned advantages associated with soft gelatine capsules (see page 16, lines 33-34) or with the choice of the components in the context of capsules (see page 19, lines 6, 22 and 30) do not mean that such encapsulation must necessarily be used.

2.3 The opposition division found that claims 5-10 did not introduce added subject-matter because it was clear from the application as a whole that the disclosed dosage forms were intended for oral delivery (see point 14.4 of the appealed decision). In their grounds of appeal, appellant O2 state that they maintain their objection against claims 5-10, but do not provide any reason why this finding in the appealed decision should be reversed. The Board sees no ground for setting aside the appealed decision in this respect.

2.4 Hence, auxiliary request 1 meets the requirements of Article 123(2) EPC.

3. Sufficiency of disclosure

The objections of the appellants-opponents relate to the achievement of the claimed specific immediate release profile over the whole scope of claim 1.

The Board shares the opinion of the opposition division that the appellants-opponents have not provided serious doubts substantiated by verifiable facts that the invention cannot be put into practice over the whole scope of the claims. It is not contested that the patent discloses at least one way to carry out the invention, for instance formulation P1 of paragraph [0051], which is a liquid suspension as claimed but is not formulated in a soft gel capsule. Thus the appellants-opponents' argument that the patent would provide no guidance on how to carry out the claimed invention is not convincing. Furthermore, there is no support for the assertion that claim 1 would be so broad that the skilled person cannot reproduce the invention over its whole scope.

Accordingly, the criteria of sufficiency of disclosure are met.

4. Inventive step

4.1 The parties agree that D6 represents the closest prior art.

4.2 D6 relates to nintedanib esilate and pharmaceutical compositions thereof (see page 1, lines 7-15). D6 singles out soft gelatine capsules as an especially suitable pharmaceutical formulation (see page 11, line 24, to page 12, line 4). However D6 contains no actual example of formulation.

4.3 The subject-matter of claim 1 of auxiliary request 1 differs from the teaching of D6 at least in that the dosage form comprises a viscous lipid suspension formulation of

10-50 wt% of the active substance in
10-70 wt% of MCT,
1-30 wt% of hard fat and
0.1-10 wt% of lecithin.

4.4 Technical effect and problem

4.4.1 Appellant P filed experimental data showing a significant effect of the presence of lecithin on the dissolution profile (see reply dated 2 December 2021, last two paragraphs on page 2 and page 3). A composition according to claim 1, comprising 2% lecithin, achieves an immediate release profile with more than 80% dissolution in 60 minutes under the *in vitro* conditions of Figure 2 and paragraph [0024] of the patent, which are as defined in claim 1 of auxiliary request 1 (see the blue squares curve). In contrast, the same composition lacking lecithin does not reach half of that dissolution level after 60 minutes (see the red dots curve).

The Board considers that this data credibly demonstrates a technical effect on the release rate associated with one of the differentiating features.

4.4.2 In this respect, the Board does not accept the appellants opponents' argument that the claimed immediate release profile was already implied by the unspecific mention of a soft gelatine capsule formulation in the closest prior art D6. There is no explicit mention in D6 of any release profile for these capsules. An immediate release profile as claimed, corresponding to at least 70% (Q65%) dissolution in 60 minutes *in vitro* under defined conditions, is also not the inevitable result of the soft gelatine capsules of D6 and thus cannot be regarded as implicit in the

disclosure of D6, irrespective of the alleged broadness of the claimed dissolution range. As shown in D16 (see pages 395 and 425), and as acknowledged by the appellants opponents, soft gelatine capsule formulations often lead to enhanced dissolution or immediate release but may also be designed to have delayed or enteric release profiles. A lack of indication in D6 of the precise type of soft gelatine capsule formulation cannot be regarded by default as a clear and unambiguous disclosure of an immediate release, let alone of a dissolution of 70% or more in 60 minutes.

4.4.3 Considering the Board's conclusion below, it is not necessary to assess the further alleged technical effects with respect to bioavailability, stability and inter-individual variation. The problem to be solved is thus the provision of an immediate release formulation of nintedanib.

4.5 Obviousness

4.5.1 It is not contested that the carrier components recited in claim 1 (MCT, hard fat and lecithin), and their use for formulating suspensions for soft gelatine capsules, were part of common general knowledge at the priority date. In particular, the use of lecithin in suspensions for soft gel capsules is reported in D2 (as a wetting agent for the determination of base absorption, see page 403, right-hand column, second-last paragraph), D3 (to optimise flowability, see page 62, chapter 2.2, lines 13-14), D4 (in oral suspensions at a concentration of 0.25-10%, see page 409, table 1) and D15 (as emulsifying agent, see page 88 under "Phospholipids").

The relevant question is however whether the prior art would have motivated the skilled person to combine the claimed components in the claimed amounts in the expectation of solving the technical problem. This question must be answered in the negative, because the prior art contains no hint that the addition of lecithin in the claimed amounts would have such a significant effect on dissolution and would allow the achievement of the claimed immediate release properties. There is in particular no basis for the appellants opponents' contention that the wetting properties mentioned in D2 would be equated with an effect on solubilisation, as opposed to being related to contact angle on surfaces.

- 4.5.2 The appellants-opponents further argue that the skilled person reading D6 would have turned to the document D7 cited therein as regards the soft gelatine capsule formulation, and that D7 disclosed the claimed ingredients. The Board does not share this view either.

Firstly, the relevant passage of D6 (see page 11, line 28, to page 12, line 4) states:

"An especially suitable pharmaceutical formulation for the compounds in accordance with the present invention is soft gelatine capsules. Suitable soft gelatine capsules for the encapsulation of pharmaceutical compounds and the process for their preparation are described, for example," followed by references to D26, D27, D28 and D7 among others.

As argued by respondent P, the wording "for the encapsulation" does not indicate that the subsequent references relate to the formulation of the capsule filling (i.e. in the present case, the liquid suspension), but rather to the composition of the

encapsulating gelatine shell. This is confirmed by the fact that most references in this passage of D6 (i.e. D26-D28) only disclose shell compositions, and processes for their preparation, but no filling formulation. In this list, only example 3 of D7 discloses a soft gelatine capsule filling formulation, albeit applied to a different active pharmaceutical ingredient (namely oxytetracycline). Accordingly, there is no motivation in D6 for the skilled person to turn to any of the references therein for the formulation of the liquid suspension filling, or to use the formulation of example 3 of D7 as such for the different active ingredient nintedanib esilate.

Secondly, example 3 of D7 describes soft gelatine capsules of crystalline oxytetracycline containing an inert fill comprising Miglyol 812 (an MCT in the sense of the patent, see paragraph [0042]), bees wax, hydrogenated vegetable oils and soy lecithin. D7 however neither discloses the amounts of these components, nor the use of a hard fat. There is no evidence that the hydrogenated vegetable oils mentioned in D7 generally qualify as hard fat. At most, D29 shows that the two expressions overlap, namely that softisan (or at least some compounds of this class) can be considered both as hydrogenated vegetable oil and as hard fat. Thus, considering that document D29 does not modify the conclusion above, it is not necessary to give the reasons for its admission.

Lastly, there is still no incentive in D6 or D7 to use a composition comprising the ingredients recited in claim 1, in particular lecithin, in the expectation of solving the technical problem and obtaining the technical effect on dissolution and release profile observed above.

4.6 Accordingly, the subject-matter of auxiliary request 1 involves an inventive step.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The case is remitted to the opposition division with the order to maintain the patent on the basis of auxiliary request 1 filed during the oral proceedings on 15 June 2023.

The Registrar:

The Chairman:



K. Boelicke

A. Usuelli

Decision electronically authenticated