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Datasheet for the decision of 25 January 2022

Case Number: T 2591/18 - 3.3.07

Application Number: 07820560.6

Publication Number: 2068839

IPC: A61K9/16, A61K31/506, A61P35/02

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITIONS COMPRISING NILOTINIB OR ITS SALT

Patent Proprietor:
Novartis AG

Opponents:
Generics [UK] Limited
Strawman Limited
Fresenius Kabi Deutschland GmbH
medac Gesellschaft für klinischeSpezialpräparate mbH

Headword:
Pharmaceutical compsitions comprising nilotinib/NOVARTIS

Relevant legal provisions:
EPC Art. 123(2), 56
RPBA 2020 Art. 13(2)

Keyword:
Amendments - allowable (yes)
Admission of arguments on inventive step (Yes)
Main request - Inventive step (Yes)

Decisions cited:
T 0247/20

Europäisches Patentamt
European Patent Office
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Beschwerdekammern

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Case Number: T 2591/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 25 January 2022

Appellant: (Opponent 1)	Generics [UK] Limited Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
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Appellant: (Opponent 2)	Strawman Limited Orchard Lea Horns Lane Combe, Witney Oxfordshire OX29 8NH (GB)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Appellant: (Opponent 3)	Fresenius Kabi Deutschland GmbH Else-Krömer-Strasse 1 61352 Bad Homburg (DE)
Representative:	Fresenius Kabi Deutschland GmbH Patent Department Borkenberg 14 61440 Oberursel (DE)
Respondent: (Patent Proprietor)	Novartis AG Lichtstrasse 35 4056 Basel (CH)

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Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 18 September 2018 concerning maintenance of the European Patent No. 2068839 in amended form.**

Composition of the Board:

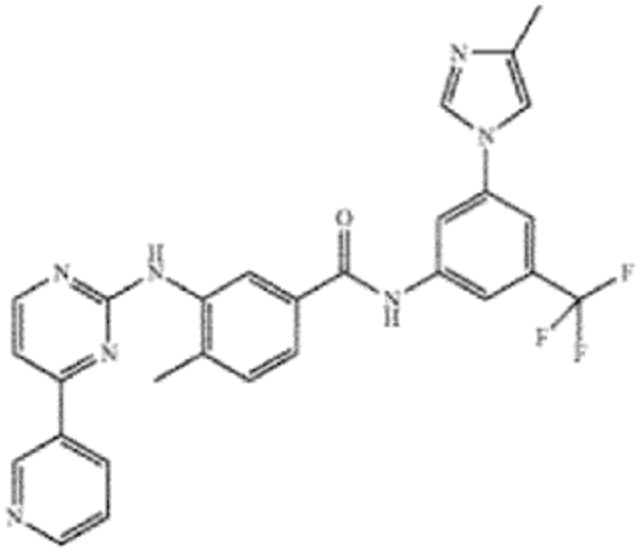
Chairman A. Usuelli
Members: D. Boulois
L. Basterreix

Summary of Facts and Submissions

I. European patent No. 2 068 839 was granted on the basis of a set of 13 claims.

Independent claim 1 as granted read as follows:

"1. A pharmaceutical composition, in the form of a capsule comprising:
a granule comprising a therapeutic compound in an intimate mixture with at least one pharmaceutically acceptable excipient, wherein said therapeutic compound is
4-Methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]-N[5-(4-methyl-1 H-imidazol-1-yl)-3-(trifluoromethyl)phenyl] benzamide:



or a pharmaceutically acceptable salt thereof, and wherein said granule further comprises a surfactant, and

wherein said pharmaceutical composition comprises a lubricant, and the concentration of said lubricant does not exceed 1% by weight of the pharmaceutical composition."

II. An opposition was filed under Article 100 (a), (b) and (c) EPC against the granted patent on the grounds that the subject-matter of the granted patent lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the application as filed.

III. The appeal lies from the decision of the opposition division finding that the patent in amended form met the requirements of the EPC. The decision was based on the main request filed with letter of 12 December 2016 as auxiliary request 1.

In comparison to claim 1 as granted, claim 1 of the main request was amended by the feature **"and wherein said surfactant is poloxamer"**.

IV. The documents cited during the opposition proceedings included inter alia the following:
D3: WO 2004/005281
D5: Drugs and the pharmaceutical Sciences, Handbook of Pharmaceutical Granulation Technology, Swarbrick
D5a: page 102 of D5
D6: Aulton M. E./"Pharmaceutics: The Science of Dosage Form Design" Churchill Livingstone, London 1988
D6a: page 330 of D6
D7: Wade A, and Weller P. J., "Handbook of Pharmaceutical Excipients", The Pharmaceutical Press London 2000
D8: BASF Brochure
D9: WO 01/08686

D10: EP 0 925 294 B1
D11: WO 2005/025566
D12: WO 2006/013444
D14: Nateglinide - US label
D15: "Modern Pharmaceutics", edited by G.S. Baker, C.T. Rhodes, Marcel Dekker, 4th Edition, 2002
D16: S. Stegemann in "Hard gelatin capsules today- and tomorrow", Capsugel Library, 2nd edition 2002
D17: "Pharmaceutical Capsules" edited by F. Podczeck, B.E. Jones, Pharmaceutical Press, 2nd edition, 2004.
D18: "Lehrbuch der Pharmazeutischen Technologie", edited by K.H. Bauer, K-H. Fromming, C. Fuhrer, Wissenschaftliche Verlagsgesellschaft mbHStuttgart, 7. Auflage 2002
D19: "Remington: The Science and Practice of Pharmacy", volume 1, chapter 45, Lippincott, Williams and Wilkins, 20th edition, 2001
D20: "Encyclopaedia of Pharmaceutical Technology", volume 9, Marcel Dekker, 1994
D21: B. Jones in "Two-piece gelatin Capsules: excipients for powder products,European practice", Pharmaceutical Technology Europe, 1995, vol. 11 (November), p.25-34
D22: WO 2007/015871
D23: "Handbook of Pharmaceutical Excipients", edited by A. H. Kibbe, Pharmaceutical Press, 3rd edition, 2000
D24: "Remington, The Science and Practice of Pharmacy", chapter 76, Mack Publishing Company, 17th edition, 1985
D31: Schoffiing, Arzneiformenlehre, 3. AufL, Deutscher Apotheker Verlag, Stuttgart, 1998, p. 168-175
D32: Hunnius, Pharmazeutisches Worterbuch, 9. AufL, de Gruyter, Berlin, 2004, p. 939
D33: Lieberman, Pharmaceutical Dosage Forms, Vol. 1, Marcel Dekker, New York, 1980, p. 129-130

D34: Voigt, Pharmazeutische Technologie fur Stadium und Beruf, 7. AufL, Ullstein Mosby, Berlin, 1993, p. 234-235.
D35: Bauer, Pharmazeutische Technologie, 4. Auf., Thieme, Stuttgart, 1993, p. 292-293 and 300-301
D37: Solubility data
D38: Tasigna EMA Scientific Assessment Report (Scientific Discussion)
D39: Expert declaration of Dr. Philippe Bouillot
D40: Aulton, Pharmaceutics: The Science of Dosage Form Design, 1988, pages 330-340
D41: Aulton, Pharmaceutics: The Science of Dosage Form Design 2002
D42: Rowe R. C. et al, The Handbook of Pharmaceutical Excipients 2006
D43: Rowe R. C. et al, The Handbook of Pharmaceuticals Excipients 2006
D44: Singhare D.S. et al. Poloxamers Block Copolymers in Drug Delivery 2005
D47: Declaration of Philippe Bouillot (Poloxamers)
D48: Handbook of Pharmaceutical Excipients, fifth Edition, pages 580-584.

V. According to the decision under appeal, the main request met the requirements of Article 123(2) EPC, Article 83 EPC and 54 EPC.

With regard to inventive step, the disclosure of hard capsules containing the claimed therapeutic compound, i.e. nilotinib, in granules in D3 was considered the closest state of the art. The subject-matter of claims 1, 6 and 12 differed from the hard capsules of D3 in that:
- specifically, poloxamer was claimed as a surfactant,
- said surfactant was present in granules, and

- a percentage range of lubricant was indicated, i.e. "does not exceed 1 %".

In view of example 2 of the patent and D37, a good dissolution and stability was demonstrated. The objective problem underlying claims 1, 6, and 12 was to provide a nilotinib granule composition suitable for a hard capsule further characterised by adequate dissolution and adequate stability of nilotinib. None of the cited documents gave a pointer to an improvement of dissolution or stability in relation to poloxamer. The claimed subject-matter was inventive for this reason.

VI. Opponent 01, opponent 02, and opponent 03 (hereinafter appellants 01, 02 and 03) filed an appeal against said decision. With its statement setting out the grounds of appeal appellant 01 submitted the following items of evidence:

A5b: Drugs and the Pharmaceutical Sciences, Handbook of Pharmaceutical Granulation Technology, Second Edition, Ed. J. Swarbick, Taylor & Francis, 2005, pages 407-429

A49: V. Jannin et al., International Journal of Pharmaceutics, 2006, 309, 6-15 (available online 20 December 2005).

VII. With its reply to the statements setting out the grounds of appeal, the patent proprietor (hereinafter the respondent) submitted the following item of evidence:

A50: Pharmaceutics: The Science of Dosage Form Design, Aulton, 2nd ed., 2002, p. 136

VIII. A communication from the Board, dated 30 September 2021, was sent to the parties.

IX. Oral proceedings took place on 25 January 2022.

X. The arguments of the appellants may be summarised as follows:

Main request - Amendments

According to appellant 02, claim 1 did not have a direct and unambiguous basis in the application as filed. Poloxamer in original claim 8 was dependent on the level of surfactant in claim 5.

Admission of the arguments submitted by Appellant 01 in his letter dated 17 December 2021

The arguments objected by the respondent were reasonable reactions to developments in the proceedings, in particular brought by the respondent in its reply to the statement of grounds of appeal.

Main request - Inventive step

D3 was considered as the closest prior by all appellants.

According to appellants 01 and 02, the disclosure in the final paragraph of page 34 of D3 constituted the closest prior art. This paragraph disclosed hard capsules containing the claimed active ingredient (nilotinib) in the form of granules admixed with other excipients. The presence of poloxamer as the surfactant and less than 1% lubricant were the distinguishing features. The technical effects resulting from these features, which were shown in Example 2 of the patent and Part B of D37, demonstrated a better dissolution for a capsule containing poloxamer as a surfactant.

According to appellant 01, the technical problem was merely the provision of a further nilotinib composition because the results for poloxamer 188 shown in D37 could not be extrapolated across the whole class of surfactants.

According to appellant 02, the problem was the provision of a nilotinib granule composition suitable for hard capsule further characterised by adequate dissolution and adequate stability of nilotinib.

According to appellant 03, the problem was the provision of an alternative formulation.

The solution was obvious since the person skilled in the art would have achieved the claimed effects by the application of routine techniques to the disclosure of D3. Such techniques were disclosed for instance in D24. Moreover, the addition of a lubricant was a routine measure for the skilled person, and the addition of a surfactant was known from D5. Further pointers for the use of poloxamer were given in D44 and A49, and D18 showed that the granulation was also known.

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

Main request - Amendments

Poloxamer was described as the preferred surfactant in the application as filed on page 2, and was also present in claim 8 and in the specific formulation example.

Admission of the arguments submitted by Appellant 01 in his letter dated 17 December 2021

The appellant 01 had three new arguments regarding inventive step in its last letter which constituted an amendment to its case which should not be admitted.

Main request - Inventive step

Example 97 of D3 was the closest prior art. There were numerous dosage forms described on pages 33-35 of D3. The distinguishing features with the claimed subject-matter were:
(i) the active ingredient is nilotinib;
(ii) the active ingredient is in the form of granules;
(iii) the granules contain a poloxamer;
(iv) the capsule contains a lubricant in less than 1% by weight; and
(v) the granules contain an excipient in addition to a poloxamer.
The technical effects resulting from the differences were that the claimed composition was stable and it possessed excellent dissolution and bioavailability properties. The objective technical problem to be solved was to provide a stable dosage form of nilotinib which possesses excellent dissolution and bioavailability properties. In view of the BCS Class of nilotinib, the skilled person would have been motivated to provide a liquid formulation and in view of the hygroscopicity, the skilled person would have sought a soft gelatin capsule formulation over a hard capsule. The only example of a dosage form in the closest prior art D3 was a soft capsule in Example 97, in which the active ingredient is suspended in liquid. The general teaching of D3 is that liquid compositions were preferred. Thus, claim 1 was inventive because the

skilled person would not have sought to solve the problem by providing nilotinib in the form of granules.

XII. Requests

Appellants (opponents) 01, 02 and 03 requested that the decision under appeal be set aside and that the European patent No 2068839 be revoked.

The respondent (patent proprietor) requested that the appeal be dismissed and that the patent be maintained on the basis of the main request, or alternatively that the patent be maintained according to one of auxiliary requests 1, 2a-16a, 2b-16b or 1c to 16c filed during the opposition proceedings. It further requested that the arguments submitted by Opponent 1 in his letter dated 17 December 2021 not be admitted.

Reasons for the Decision

1. Main request - Article 123(2) EPC

1.1 The introduction of the feature "wherein the surfactant is poloxamer" in claim 1 of the main request has been objected to by appellant 02.

1.2 The use of a poloxamer as preferred surfactant is disclosed directly and unambiguously on page 2, line 1, of the application as filed. This disclosure is independent from the disclosure of the concentration of poloxamer and states *expressis verbis*: "an example of a particularly useful surfactant, is a poloxamer such as poloxamer 188".

Consequently, the introduction of the feature "wherein the surfactant is poloxamer" in claim 1 finds a direct basis in the original application and the main request meets the requirements of Article 123(2) EPC.

2. Admission of the arguments submitted by Appellant 01 in his letter dated 17 December 2021

2.1 The respondent objected the admittance of three specific arguments as regards the assessment of inventive step which were brought forward by appellant 01 in its letter dated 17 December 2021.

The particular arguments objected to by the respondent were the following:
a) The recognition that the skilled person would identify nilotinib as having low solubility and permeability, and as having a "slight hygroscopic tendency" (see letter of 17 December 2021, page 1, 4th paragraph).
b) The observation that the patent only identifies nilotinib as having a "slight hygroscopic tendency" and that D15 teaches the solution to this problem (see letter of 17 December 2021, page 3, 1st paragraph).
c) The discussion on D15 with regard to the BCS classification of the drugs, with the example of hydrochlorothiazide and the discussion on the factors taken in account when formulating this active ingredient in hard capsules (see letter of 17 December 2021, page 2, two last paragraphs).

2.2 In the present case, the Board issued the summons to oral proceedings in May 2021. Hence, the notification of the summons occurred before appellant 01 filed its submissions on inventive step with the letter of

December 2021. This means that Article 13(2) RPBA 2020 is relevant (Article 25(3) RPBA 2020). That provision indicates that: "Any amendment to a party's appeal case made...after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned."

2.3 The Board concurs with the interpretation of Article 13(2) RPBA 2020 given in decision T 247/20 (Reasons 1.3) and the two-fold test under Article 13(2) RPBA 2020 given therein. The first question of said test is whether the submission objected to is an amendment to a party's appeal case. If that question is answered in the negative, then the Board has no discretion not to admit the submission. If, however, that question is answered in the positive, then the Board needs to decide whether there are exceptional circumstances, justified by cogent reasons, why the submission is to be taken into account.

2.4 In the present case, the appellant 01 presented arguments with regards to the BCS class of nilotinib and the corresponding physico-chemical properties of nilotinib lengthways in its statement of grounds of appeal and also discussed the content of document D15 in the same framework. These arguments are therefore not novel and a mere development on this subject cannot constitute a case amendment, since it remains in the initial framework. Indeed as explained in T247/20, a party may always refine its arguments, even build on them, provided it stays within the framework of the arguments, and of course the evidence, submitted in a timely fashion during the proceedings.

Moreover, the Board considers that also the arguments with regard to the hygroscopic properties of nilotinib do not constitute an amendment to appellant's 01 case, for the reasons set out below.

The physico-chemical properties of nilotinib, with regard *inter alia* to the stability of the formulation, and the adequacy of hard capsules for the formulation of nilotinib, was discussed by appellant 01 in its statement of grounds of appeal (see point (47) of the statement of grounds of appeal).

The contested patent mentions the "slight hygroscopic tendency" of nilotinb in paragraphs [0048] and [0050] and its relationship with the physical stability of the filled hard capsule. This aspect was discussed by the respondent in its reply to the statement of grounds of appeal, in the same context of the arguments relating to the stability of the formulation and the adequacy of hard capsules (see *inter alia* points 3.33 and 3.34 of the reply to the grounds of appeals).

Accordingly, the appellant's 01 arguments based on the "slight hygroscopic tendency" of nilotinib are linked with the discussion on stability of the filled hard capsule and constitute also a further development of the arguments already presented with the grounds of appeal. Moreover, they were submitted to counter the arguments of the respondent in its reply to the appeal. Said arguments stay therefore within the framework of the arguments presented in relation *inter alia* to the stability of the formulation, and for this reason cannot constitute a case amendment.

2.5 Consequently, the Board has no discretion not to admit the arguments submitted by appellant 01 in its letter dated 17 December 2021.

3. Main request - Inventive step

3.1 The invention relates to a pharmaceutical composition in the form of a capsule with a granule comprising nilotinib and poloxamer as surfactant, wherein the composition comprises less than 1% by weight of a lubricant. Nilotinib and its salts are poorly water-soluble compounds and are difficult to formulate and deliver (see the specification, paragraph [004]).

3.2 D3 is considered as the closest prior art by all parties.

D3 discloses the preparation of inhibitors of tyrosine kinase. Nilotinib is disclosed in example 92 and on page 23 among several other compounds. The description on pages 33-35 mentions the preparation of various compositions suitable for the administration of the inhibitors of tyrosine kinase, such as tablets, ampoules, vials, suppositories, capsules, ointments, creams, pastes, foams, tinctures, sprays, etc...Examples are capsules containing about 0.05 g to about 1.0 g active ingredient (see page 33, lines 20-21).

Hard capsules which may contain the active ingredient in form of granules are mentioned on page 34 last paragraph, said passage reading:
"Pharmaceutical compositions for oral administration also include hard capsules consisting of gelatin, and also soft, sealed capsules consisting of gelatin and a plasticizer. The hard capsules may contain the active

ingredient in the form of granules, for example in admixture with fillers, binders, and/or glidants, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in suitable liquid excipients, to which stabilizers and detergents may also be added."

Example 97 of D3 discloses the preparation of soft capsules, each comprising one of the inhibitor of tyrosine kinase mentioned in the preceding examples. The active ingredients are ground in a wet pulverizer with propylene glycol laurate to produce particles.

Appellants 01 and 02, as well as the opposition division in its decision, considered that the last paragraph of page 34 constituted a suitable starting point for assessing inventive step, while in the respondent's view, it was example 97. In view of the number of technical features in common with the subject-matter of claim 1 of the main request the Board concurs with the appellants' view.

The passage on page 34 of D3 does not disclose a composition with poloxamer as surfactant, and with an extra-granular lubricant at a concentration not exceeding 1% by weight.

3.3 According to the opposition division in its decision, the problem to be solved is to provide a nilotinib granule composition suitable for a hard capsule further characterised by adequate dissolution and adequate stability of nilotinib. The appellant 02 made its assessment on inventive step on the basis of the problem as defined by the opposition division.

The problem as defined by the respondent is the provision of a physically stable dosage form of nilotinib which possesses excellent dissolution properties.

The problem as seen by appellant 01 is the provision of a further nilotininb composition, while appellant 03 sees the problem as the provision of an alternative composition of nilotinib.

3.4 The solution to any of these problems is a composition comprising in particular a lubricant, the concentration of said lubricant does not exceed 1% by weight of the pharmaceutical composition, and a surfactant, wherein the surfactant is a poloxamer.

3.5 The respondent relied on some passages of the description and on the examples of the specification as well as on the experimental tests D37 to demonstrate the existence of an effect.

3.5.1 Example 2 of the patent shows that a capsule comprising a granulate of nilotinib hydrochloride monohydrate with 0.8% by weight of poloxamer 188, and 0.5% by weight of an extra-granular lubricant as prepared in example 1, has a dissolution rate of 99.1% in 60 minutes.

The results of example 2 are confirmed in Part B of D37, wherein the formulation 2 comprising poloxamer 188 has the same dissolution rate. D37 provides a further comparison of the dissolution rate with other compounds, namely PEG 4000 (Formulation 1, 100% of dissolution after 60 minutes), sodium lauryl sulfate (Formulation 3, 67% of dissolution after 60 minutes), HPMC (Formulation 4, 87% of dissolution after 60 minutes), HPC (Formulation 5, 94% of dissolution after

60 minutes). These experiments show clearly that poloxamer provides better dissolution properties than another surfactant, namely sodium lauryl sulfate, and than polymers such as HPMC or HPC.

In view of these experiments, it is therefore credibly shown that the composition as claimed shows an improved dissolution linked in particular with the presence of poloxamer.

3.5.2 Appellants 01 and 02 argued that the problem of the improvement of the dissolution properties has not been solved across the scope of claim 1 because the data relate to a specific poloxamer (poloxamer 188), whereas claim 1 refers to poloxamers in general.

The respondent filed document D47 in response to this argument, which shows that most poloxamers are solid at ambient temperature and have a very close HLB value as shown by the following tables:

Poloxamer	Physical appearance	Melting point (°C)
Poloxamer 124	Liquid	16
Poloxamer 188	Solid	52-57
Poloxamer 237	Solid	49
Poloxamer 338	Solid	57
Poloxamer 407	Solid	52-57

Poloxamer	HLB value
Poloxamer 124	16
Poloxamer 188	29
Poloxamer 237	24
Poloxamer 338	27
Poloxamer 407	22

It appears therefore credible that an adequate dissolution can be obtained with all poloxamers, and that the problem to provide a nilotinib granule composition suitable for a hard capsule characterised by an adequate dissolution is solved. An evidence of the contrary has in any case not been provided by the appellants.

3.5.3 With regard to the stability, the application as filed does not make any reference to the chemical stability of nilotinib, as argued by appellant 01. Paragraph [0050] was cited by the respondent as a basis for this technical problem, but this passage appears to refer to the physical stability of the filled hard gelatin capsule and its possible deformation, and is not about the formation of degradation products of nilotinib or a possible incompatibility of nilotinib with an excipient. The problem of chemical stability is therefore not taken in consideration when assessing inventive step.

With regard to the physical stability of the dosage form, paragraph [0050] of the patent mentions that "because of the slight hygroscopic tendency of the nilotinib hydrochloride monohydrate, it may be expected that the filled hard gelatin capsule shells would deform over aging" but that "surprisingly, the physical stability of the filled hard gelatin capsules did not substantially deform during visual inspection during accelerated aging". The passage of paragraph [0050] further point out that "preferably, in order to achieve this stability, the water content of the capsules should so low that upon drying the capsules for 10 min at 80 °C the loss of weight should be lower than 3.0 %", an optional feature not present in claim 1 of .

Accordingly, the physical stability has been achieved with the use of the hard capsule, which is also the type of dosage form disclosed in document D3 on page 34. Accordingly, it is not possible to conclude to an improvement of the physical stability over the closest prior art.

Thus, in the Board's view, the technical problem can be formulated as the provision of a nilotinib granule composition suitable for a hard capsule characterised by an adequate dissolution.

3.6 It remains to determine whether the claimed solution, namely the use of a composition comprising a lubricant, the concentration of said lubricant not exceeding 1% by weight of the pharmaceutical composition and a surfactant, wherein the surfactant is a poloxamer, for providing improved dissolution properties is obvious.

3.7 With regard to obviousness, appellant 01 mentioned documents D5, D6, D15, D19, D24, D43, D44, A49, while appellant 02 mentioned D7, D9-D12, D15, D24, D41, and appellant 03 mentioned D5-D8, D15-D21, D23, D24, D31-D35.

D5 relates to various granulation techniques, as well as D6 which mentions also the use of wetting agents, such as sodium lauryl sulfate in capsule formulations (see page 327).

D7 is a common general knowledge document on pharmaceutical excipients and the cited passages relate to silicon dioxide, lactose, magnesium stearate, poloxamer, and povidone, as well as their possible use in pharmaceutical dosage forms.

D8 is a technical information sheet on poloxamer 188, while D44 relates to applications of poloxamers in pharmaceutical formulations.

D9-D12 are patent documents disclosing the use of poloxamer and/or magnesium stearate in solid pharmaceutical compositions.

D15-D17 are general documents dealing with pharmaceutical capsules and D18, D19, D31-D35, D41 are common general knowledge documents relating to pharmaceutical technology or relating to the use of common excipients.

D19 is a general document on oral dosage forms, the techniques of preparation thereof and the excipients used therefor.

D23 is a common general knowledge document relating to pharmaceutical excipients, namely, silicon dioxide, lactose, magnesium stearate, poloxamer, and povidone.

D24 is a general common knowledge document relating to the pre-formulation steps of pharmaceutical compositions.

D31-D35 are documents of common general knowledge on pharmaceutical technology.

D43 is a monography on poloxamer which gives inter alia a list of all possible functions of poloxamer in pharmaceutical compositions, such as in particular as emulsifying agent.

A49 is a scientific article on the influence of poloxamer in the dissolution properties of compositions comprising lipid matrices of Precirol®.

3.7.1 It results from the teaching of all these cited documents that the preparation of capsules comprising granules, as well as the use of poloxamer and of a lubricant in the claimed concentration were generally known, a fact which was anyway not contested by the respondent.

However, the Board notes that D3 discloses a capsule comprising a granulate only as a possible option among numerous other alternatives. Even if it may be understood from D3 that the compounds of formula I present solubility issues, the teaching of D3 directs the skilled person rather to a formulation in liquid form, since it is explicitly disclosed that "preference is given to the use of solutions of the active ingredient, and also suspensions or dispersions" (see D3, page 33, 5th paragraph). Furthermore, D3 does not provide any pointer to use a surfactant in solid dosage forms, let alone poloxamers. In particular, there is no teaching neither in D3 nor in any other cited document that poloxamer would provide the best dissolution profile for the poorly soluble nilotinib, as shown in D37. There is also no clear indication in D3 as to whether the excipients should be included in the granules or mixed with them. The generic statement on page 34 does not specify this.

3.7.2 The Board can also not follow the appellants' arguments that the formulation of nilotinib was a routine development process and followed a logical chain of commonly known steps. Hence, according in particular to appellant 02, the routine development of formulations

would include in particular the following steps, all seen as routine steps:
(i) Identification of nilotinib as a poorly soluble drug (routine step in D24),
(ii) Inclusion of a surfactant to improve solubility D15, D24 and others),
(iii) Routine excipient stability studies to exclude unsuitable surfactants (D24),
(iv) Decision on surfactant/lubricant (D15), and
(v) Routine dissolution study to demonstrate solubility from the composition (D24).

The Board considers however that at least steps (ii)-(iv) involve choices which have to be made within several possibilities. This results in the start of a screening and research program which implies that several decisions are to be taken among different existing effective ways to improve the solubility (e.g. changing the dosage form to a solubilised form, adding excipients such as polymers, altering the pH, adding co-solvents, etc.), then possibly among several different effective compounds that can be used to improve the solubility (e.g polymers such as shown in D37, etc.), then finally among several possible surfactants (e.g sodium lauryl sulfate, as also shown in D37, etc.). Hence, arriving at the claimed solution cannot be made without hindsight knowledge of the invention.

3.8 Accordingly, the claimed subject-matter is inventive and the main request meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated