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Datasheet for the decision of 7 May 2021

Case Number: T 1875/18 - 3.3.07

Application Number: 11707284.3

Publication Number: 2538925

IPC: A61K9/28, A61K9/48, A61K31/437, A61P7/02

Language of the proceedings: EN

Title of invention:
APIXABAN FORMULATIONS

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Headword:
Apixaban/BRISTOL-MYERS

Relevant legal provisions:
EPC Art. 123(2)

Keyword:
Amendments - intermediate generalisation

Decisions cited:
G 0002/10, T 0879/09, T 0962/98

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 1875/18 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 May 2021

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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 May 2018 revoking European patent No. 2538925 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	C. Schmidt

Summary of Facts and Submissions

I. European patent 2 538 925 (hereinafter "the patent"), was granted on the basis of 12 claims.

Claim 1 as granted related to:

"A tablet or capsule comprising a pharmaceutical composition, wherein the pharmaceutical composition comprises apixaban and a pharmaceutically acceptable diluent or carrier, wherein the apixaban is in particulate and crystalline form and the individual apixaban particles, whether the particles exist singly or are agglomerated, have a D90 equal to or less than 89 µm as measured by laser light scattering."

II. Eleven oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the application as filed.

III. The appeal filed by the patent proprietors lies against the decision of the opposition division posted on 09 May 2018 to revoke the patent. The decision was based on the main request and auxiliary requests 1-5, which were all filed with the submission of 23 January 2018.

The amended claim 1 of the main request related to:

"A tablet comprising a pharmaceutical composition, wherein the pharmaceutical composition comprises up to

5 mg apixaban and a pharmaceutically acceptable diluent or carrier, wherein the apixaban is in particulate and crystalline form and the individual apixaban particles, whether the particles exist singly or are agglomerated, have a D_{90} less than 89 µm as measured by laser light scattering, wherein the composition consists of the following components:
(a) intragranular:
apixaban, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, sodium lauryl sulfate;
(b) extragranular:
croscarmellose sodium, magnesium stearate; and
(c) a film coat;
and wherein the tablet is made using a dry granulation process."

Claim 1 of auxiliary request 1 corresponded to claim 1 of the main request except that the composition was defined to comprise 5 mg apixaban.

Claim 1 of auxiliary request 2 corresponded to claim 1 of the main request except that the composition was defined to comprise 2.5 mg apixaban.

In auxiliary requests 3-5 the product claims were deleted. Claim 1 of auxiliary request 3 related to:

"A process of manufacturing an apixaban tablet having a composition comprising up to 5 mg apixaban and a pharmaceutically acceptable diluent or carrier, wherein the apixaban is in particulate and crystalline form and the individual apixaban particles, whether the particles exist singly or are agglomerated, have a D90 less than 89 µm as measured by laser light scattering, wherein the process comprises the steps of:

(1) blending apixaban, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and sodium lauryl sulfate as raw materials prior to granulation;
(2) granulating the raw mate1ials from the step (l) using a dry granulation process;
(3) blending the granules obtained in the step (2) with croscarmellose sodium and magnesium stearate as extragranular raw mate1ials;
(4) compressing the blend from the step (3) into a tablet; and
(5) film coating the tablet from the step (4)."

The independent claims of auxiliary requests 4 and 5 corresponded to claim 1 of auxiliary request 3 except that the compositions were defined as "comprising 5 mg apixaban" (auxiliary request 4) or "comprsing 2.5 mg apixaban" (auxiliary request 5).

IV. In the decision under appeal reference was *inter alia* made to the following documents:

D21: Melia et. al., Aliment. Pharmacol. Therap., 3, 513-525 (1989)

D22: Remington's Pharmaceutical Sciences, 18th edition 591 (1990)

D59 : Sucker et. al., Pharmazeutische Technologie, 2nd edition 158-161 (1991)

V. According to the decision under appeal:

(a) Claim 1 of the main request defined a tablet obtained by a dry granulation process and comprising a pharmaceutical composition comprising up to 5 mg apixaban, wherein the apixaban was in a specific particulate and crystalline form and

wherein the composition consisted of specific intragranular and extragranular components and a film coat. The application as filed mentioned in Table 3 the defined combination of the specific ingredients only in the context of their specific relative amounts. The omission of these relative amounts in the claims of the main request resulted in an unallowable intermediate generalisation, because the disclosure of the ingredients in Table 3 was inextricably linked to the disclosed relative amounts, as was evident from documents D21, D22 and D59. Hence the main request did not meet the requirement of Article 123(2) EPC.

(b) The claims of auxiliary requests 1-5 comprised the same unallowable intermediate generalisation as the claims of the main request and were therefore also not allowable under Article 123(2) EPC.

VI. In their statement setting out the grounds of appeal and their further submission of 12 June 2019 the appellants relied on the main request and auxiliary requests 1-5 on which the decision under appeal was based.

Replies to the statement setting out the grounds of appeal were filed by respondent-opponents 1, 3, 4, 5, 7, 8, 9, 10 and 11.

VII. With the summons of 29 July 2020 the Board invited the parties to attend oral proceedings on 7 May 2021 .

In a communication pursuant to Article 15(1) RPBA issued on 6 November 2020 the Board expressed the preliminary opinion that the claims of the main request

and the claims of the auxiliary requests 1-5 did not comply with the requirement of Article 123(2) EPC.

VIII. With the consent of the parties oral proceedings were held on 7 May 2021 in the form of a videoconference. The oral proceedings were attended by the appellants and the respondent-opponents 1, 3, 4, 5, 7, 8, 9, 10 and 11.

IX. The arguments of the appellants in as far as relevant to the present decision can be summarised as follows:

Claim 1 of the main request was essentially based on the tablet compositions described in paragraph [0006] with further definition of the specific components in line with Table 3.

Table 3 presented in its left column the defined components and in the middle and right column the amounts of the components in exemplified tablet compositions containing 5 mg or 20 mg apixaban. The right column explicitly described a 20 mg apixaban tablet. The middle column referred in its heading to a 5% w/w Dry Loaded Granulation, but also specified a total of 100 mg, which necessarily implied a tablet containing 5 mg apixaban. The reference to a total weight of 100 mg was consistent with the mention of the total weight of 103.5 mg for the final coated tablet and evidently did not relate to an amount in % w/w of the granulate mentioned in the heading of the middle column. The definition of the total amounts in mg in the middle column of Table 3 was clearly not an isolated error regarding the unit, as was further confirmed by a similar reference in Table 4 to a total of 103.5 mg for the ingredients of a coated tablet prepared by wet granulation intended for comparison.

This interpretation of Table 3 was further supported by the comment in paragraph [0033] that Table 3 showed a plurality of tablet compositions obtained by dry-granulation, as this indicated that the tablet of the right column was not the only tablet composition of Table 3.

The application as filed further explicitly mentioned that the presented examples were non-limiting (see paragraph [0032]). As the teaching in paragraph [0006] was not limited with respect to the excipients or their amounts, the skilled person would understand that the excipients listed in the left column of Table 3 exemplified a suitable combination of excipients for the tablet composition of paragraph [0006]. The question whether the amounts of the excipients influenced inventive effects of the claimed compositions was not an issue in the assessment of amendments under Article 123(2) EPC. Applying the principles established in T 962/98 and T 879/09 claim 1 of the main request therefore complied with the requirement of Article 123(2) EPC.

X. The arguments of the respondent-opponents 1, 3, 4, 5, 7, 8, 9, 10 and 11 in as far as relevant to the present decision can be summarised as follows:

The tablet compositions comprising up to 5 mg apixaban mentioned in paragraph [0006] were not exemplified in Table 3 of the application as filed, which only referred to a tablet containing 20 mg apixaban. The middle column related according to its heading explicitly to a "5% w/w Drug Loaded Granulation", not to a tablet. The tablet compositions of paragraph [0006] could therefore not be further characterized by features from Table 3.

Even if the content of Table 3 were considered as exemplification of the tablet compositions of paragraph [0006], it described the combination of the relevant components only in specific relative amounts. The abstraction of the combination of the components in claim 1 of the main request from the relative amounts of these excipients as disclosed in Table 3 represented an intermediate generalisation that was not allowable under Article 123(2) EPC.

The claims of the auxiliary requests were based on the same generalisation from Table 3 as in claim 1 of the main request and were therefore not allowable for the same reason.

XI. The appellants requested that the decision under appeal be set aside with the conclusion that the subject-matter claimed in the main request or in auxiliary requests 1-5, all filed with the submission of 23 January 2018, meets the requirements of Article 123(2) EPC and that the case be remitted to the first instance for reviewing the further grounds of opposition raised under Articles 100(a) and 100(b) EPC.

XII. The respondent-opponents 1, 3, 4, 5, 7, 8, 9, 10 and 11 requested that the appeal be dismissed.

The respondent-opponents 3 and 7 further requested that the case not be remitted to the opposition division.

The respondent-opponent 5 further requested that the case be remitted, in the event that the Board would allow any aspect of the appeal.

The respondent-opponents 10 and 11 further requested that issues of clarity be considered during the appeal procedure.

The respondent-opponents 2 and 6 did not present any substantive reply or request during the appeal proceedings.

Reasons for the Decision

Main request

1. Article 123(2) EPC

1.1 Claim 1 as amended in accordance with the main request defines a tablet prepared by dry granulation comprising a pharmaceutical composition, which comprises up to 5 mg apixaban and an acceptable diluent or carrier, wherein the apixaban is in particulate and crystalline form and the individual apixaban particles,existing singly or are agglomerated, have a D_{90} less than 89 µm as measured by laser light scattering.

This composition is according to claim 1 of the main request further defined to consist of apixaban, lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, magnesium stearate and sodium lauryl sulfate as intragranular components, croscarmellose sodium and magnesium stearate as extragranular components and a film coat.

1.2 The application as originally filed reports in paragraph [0006] under the heading "SUMMARY OF THE INVENTION" that compositions for tablets prepared using

a dry granulation process and comprising up to 5 mg apixaban particles having a D_{90} less than 89 µm were found to allow for consistent in-vivo dissolution, consistent exposure and consistent Factor Xa inhibition. This report is followed by the statement that accordingly the invention provides a pharmaceutical composition comprising crystalline apixaban particles of such size as measured by laser light scattering and an acceptable diluent or carrier.

In paragraph [0033] the application as filed describes tablet compositions prepared by dry granulation and used for studying bioequivalence by reference to the following Table 3:

Ingredients	Dry Granulation	
	5% w/w Drug Loaded Granulation (% w/w)	20 mg Tablet (mg/tablet)
Intragranular		
Apixaban	5.00	20.00
Lactose Anhydrous	49.25	197.00
Microcrystalline Cellulose	39.50	158.00
Croscarmellose Sodium	2.00	8.00
Magnesium Stearate	0.50	2.00
Sodium Lauryl Sulfate	1.00	4.00
Extragranular		
Croscarmellose Sodium	2.00	8.00
Magnesium Stearate	0.75	3.00
Total	100.00 mg	400 mg
Film Coat	3.5	14.0
Total	103.5 mg	414 mg

1.3 The ingredients as listed in the left column of table 3 correspond to the combination of components defined in claim 1 of the main request. The application as originally filed makes no other mention of this specific combination of components.

The definition of the tablet in amended claim 1 of the main request thus relies on features as disclosed in paragraph [0006] concerning the amount of up to 5 mg of

the apixaban in the particulate and crystalline form, which are combined with the particular choice of ingredients disclosed in the left column of Table 3.

1.4 In order to comply with the requirement of Article 123(2) EPC amendments may only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge and seen objectively and relative to the date of filing, from the original disclosure as a whole (see *i.a.* G 2/10, reasons 4.3). In line with this criterion, commonly referred to as the "gold standard", amendments corresponding to restrictions of a general original disclosure on the basis of characteristics described in the context of a more detailed embodiment are according to established jurisprudence by the Boards of Appeal of the EPO, as also relied upon by the appellants, only permissible if the skilled person would recognize without any doubt from the application as filed that the characteristics taken from the more detailed embodiment are not closely related to the other characteristics of that detailed embodiment and apply directly and unambiguously to the more general disclosure (see decision T 879/09, reasons 2.1.2-2.1.3 and T 962/98, reasons 2.5).

1.5 The Board observes that Table 3 mentions only one type of tablet explicitly, namely the "20 mg Tablet" in the right column. The middle column of Table 3 relates according to its heading to a "5%w/w Drug Loaded Granulation" defined by the amounts of the ingredients listed in the left column expressed in terms of % w/w of the granulation mass.

The isolated entries in the middle column relating to totals of "100 mg" and "103,5 mg" are not consistent

with this heading of the middle column of Table 3. The relevant ingredients actually add up to 100% and not 100 mg for the total of granulation ingredients, whilst the additional 3.5% for the film coat accounts for a total of 103.5% in relation to the granulation mass. This inconsistency in Table 3 is further underlined by the absence of a similar "100 mg" entry in the analogue Table 4, which describes tablets compositions produced by wet granulation for comparison. In view of this inconsistency the Board is of the opinion that the skilled person cannot directly and unambiguously derive a disclosure of a 5 mg apixaban tablet from the mention of "100 mg" and "103,5 mg" in the middle column of Table 3.

The appellants argued that paragraph [0033] refers to Table 3 as disclosing a plurality of tablet compositions and that the entries for the total amounts in the middle column of Table 3 necessarily relate to a 5 mg apixaban tablet to account together with the 20 mg tablet of the right column for the mentioned plurality. This argument is not considered convincing in the light of the explicit characterization of the content of the middle column of table 3 by its heading. Moreover, the plurality of tablet compositions mentioned in paragraph [0033] does not necessarily refer to tablets of different strength and may well cover the granulation composition of the middle column in addition to the actual tablets of the right column. This interpretation is further supported by the circumstance that the application as filed reports in paragraph [0035] only the testing of 20 mg apixaban tablets prepared by dry and wet granulation and makes no mention of experiments using 5 mg apixaban tablets.

1.6 The Board further observes that the tablet compositions of Table 3 are presented in paragraph [0033] of the application as filed in the context of bioaequivalence studies. As indicated in documents D21 (see pages 517, 518 and 520), D22 (page 591 right column, second paragraph) and D59 (page 160, Table 4.9) and as acknowledged in paragraph [0008] of the application as originally filed, the excipients listed in Table 3, in particular the wetting agent sodium lauryl sulfate, influence drug dissolution rates. This influence is of relevance in the context of the assessment the amendments under Article 123(2) EPC, as in view of the mentioned context of the disclosure of the compositions of Table 3 this influence indicates a functional relationship between the choice of components in the left column of Table 3 and the amounts of those components defined in the middle and right column of Table 3. Irrespective of the non-limiting purpose of the examples confirmed in paragraph [0032] of the application as filed, the skilled person would in view of this relationship not recognize without doubt that the choice of the components is unrelated to the defined amounts in Table 3 and also applies directly and unambiguously to the more generally defined compositions of claim 1 of the main request.

1.7 Considering that Table 3 does not exemplify a tablet composition comprising up to 5 mg apixaban as described in paragraph [0006] of the application as filed and defined in claim 1 of the main request (see point 1.5 above) and having regard to the relevant relationship between the ingredients and their amounts listed in Table 3 (see point 1.6 above), the Board is of the opinion that that the skilled person would not directly and unambiguously derive from the application as originally filed that the disclosure in paragraph

[0006] of the tablet compositions comprising up to 5 mg apixaban should be combined with the features of the tablet compositions of Table 3, let alone with the ingredients listed in the left column of Table 3 abstracted from their relative amounts.

Therefore the Board concludes that claim 1 of the main request does not comply with the requirement of Article 123(2) EPC.

Auxiliary requests 1-5

2. Article 123(2) EPC

Claim 1 of auxiliary requests 1 differs from the main request in that the composition is defined as comprising 5 mg instead of up to 5 mg apixaban and claim 1 of auxiliary request 2 defines the composition as comprising 2.5 mg apixaban.

Auxiliary requests 3-5 correspond respectively to the main request and auxiliary requests 2-3 with deletion of the product claims.

The claims of each of these requests involve a similar definition of a tablet composition comprising 5 mg or less apixaban in combination with the ingredients listed in the left column of Table 3 abstracted from their relative amounts as defined in claim 1 of the main request. No further argument regarding the basis for this combination in the claims of the auxiliary requests was provided by the appellants and no such basis is evident to the Board. Accordingly, the Board concludes that the claims of the auxiliary request 1-5 do not comply with the requirement of Article 123(2) EPC for the same reason as claim 1 of the main request.

Request for a decision on clarity issues

3. Following the conclusion that none of the appellants' requests can be allowed under Article 123(2) EPC issues of clarity require no further consideration.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated