Internal distribution code:

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

Datasheet for the decision of 31 January 2024

Case Number: T 2009/22 - 3.3.07

Application Number: 17175788.3

Publication Number: 3251660

IPC: A61K9/20, A61K31/4545, A61P7/02

Language of the proceedings: EN

Title of invention:
APIXABAN FORMULATIONS

Patent Proprietor:
Bristol-Myers Squibb Holdings Ireland Unlimited Company
Pfizer Inc.

Opponents:
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
Zentiva k.s.
Kutzenberger Wolff & Partner
Medichem S.A.
Teva Pharmaceutical Industries Ltd
Sandoz AG
Generics (U.K.) Limited
STADA Arzneimittel AG

Headword:
Apixaban III/Bristol-Myers

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Europäisches Patentamt
European Patent Office
Office européen des brevets

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 2009/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 31 January 2024

Appellant: (Patent Proprietor 1)	Bristol-Myers Squibb Holdings Ireland Unlimited Company Hinterbergstrasse 16 6312 Steinhausen (CH)
Appellant: (Patent Proprietor 2)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Respondent: (Opponent 1)	ZAKLADY FARMACEUTYCZNE POLPHARMA S.A. ul. Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Zentiva k.s. U kabelovny 130 10237 Praha 10 (CZ)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)

Respondent: (Opponent 3)	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Representative:	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Respondent: (Opponent 4)	Medichem S.A. Avda. Pirineus - Polígon Industrial 17460 Celrà (Girona) (ES)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Opponent 5)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Opponent 8)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Opponent 9)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Opponent 10)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Kernebeck, Thomas Kernebeck Patentanwalts GmbH Stiftstraße 2 60313 Frankfurt am Main (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 June 2022**

revoking European patent No. 3251660 pursuant to Article 101(3)(b) EPC.

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

I. European patent 3 251 660 ("the patent") was granted on the basis of eleven claims.

Claim 1 as granted defined a composition comprising up to 5 mg crystalline apixaban particles having a D_{90} less than 50 µm as measured by laser light scattering apixaban and a pharmaceutically acceptable diluent or carrier wherein the composition is prepared using a dry granulation process.

II. Ten oppositions were originally filed against the grant of the patent ("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 (earlier) application as filed. Opponents 6 and 7 withdrew their oppositions during the proceedings before the opposition division.

III. The patent proprietors filed the appeal against the decision of the opposition division to revoke the patent.

The decision of the opposition division was based on the patent proprietors' main request and auxiliary requests 1-8, which had originally been filed as auxiliary requests 2-10 on 24 March 2021.

Claim 1 of the main request defined:

"A tablet comprising a composition comprising up to 5 mg crystalline apixaban particles having a D_{90} less

than 50 µm as measured by laser light scattering and further comprising a pharmaceutically acceptable diluent or carrier wherein the composition is prepared using a dry granulation process, wherein the formulation exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the result is established as an average of 6 tablets and wherein the dissolution test is performed in 900 mL of dissolution medium containing 0.05 M sodium phosphate at pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm."

Auxiliary requests 1-3 additionally defined in claim 1 that the tablet comprised from 2.5 mg to 5 mg (auxiliary request 1), 2.5 mg or 5 mg (auxiliary request 2), or 5 mg apixaban (auxiliary request 3).

Auxiliary request 4 additionally defined with respect to auxiliary request 3 the tablet for use in the treatment of a thrombotic disorder.

Auxiliary request 5 additionally defined with respect to auxiliary request 3 the tablet for use in the treatment of a thrombotic disorder wherein the tablet is administered orally twice a day.

Auxiliary request 6 additionally defined with respect to auxiliary request 5 that the apixaban particles have a D_{90} of less than 25 µm.

Claim 1 of auxiliary requests 7 and 8 defined a process of manufacturing apixaban tablets involving a dry granulation process.

In its decision the opposition division cited *inter alia* the following documents:

D5: US 2006/0160841 A1
D8: WO 2010/147978 A1
D9: Pharmaceutical Research, 1995, 12(3), 413-420
D25: Pharmaceutics: The Science of Dosage Form Design, Aulton, 1988, 1-13, 135-173
D26: Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Form, FDA, 1997, 1-11 and A-1/A-2
D32: Clinical Pharmcology and Biopharmaceutics Review, 15 February 2012 (Center for drug evaluation and research, application number 202155Orig1s000)
D38: Pharmaceutical Dosage Forms: Tablets, volume 1, 2nd ed., 1989, 1-24
D40: Molecular Pharmaceutics, 2010, 7(4), 1235-1243
D48: Modern Pharmaceutics, Chapter 10 "Tablet Dosage Forms", Marcel Dekker (G. S. Banker and C. T. Rhodes, Eds., 3rd ed., 1996), 333-359,
D61: Pharmaceutics: The Science of Dosage Form Design, Aulton, 3rd ed., 2007, 286-291 and 443-449
D65: ClinicalTrials.gov, NCT00633893, 18 February 2010
D72: European Medicines Agency, Committee for Medicinal Products for Human Use, Guidelines on the investigation of bioequivalence, 2010, pages 1/27-27/27
D74: European Journal of Pharmaceutical Sciences, 1999, 9, 117-121
D75: Pharmaceutical Research, 2002, 9(7), 921-925
D80: Encyclopedia of Pharmaceutical Technology, Volume 3, Marcel Dekker Inc., 2002, Chapter "Tablet Formulation", 2701-2712
D81: The AAPS Journal, 2008, 10(2), 306-310
D82: Journal of Pharmaceutical Sciences, 2004, 93(6), 1375-1381

D88: Guidance for Industry, U.S. Department of Health and Human Services, August 2000,1-13
D93: Declaration of Dr. Jatin Patel, dated 5 May 2017
D96: Expert declaration of Prof. Dr. Henning Blume, dated March 2017
D97: Annual Report 2017 (Form 10-K) of Bristol-Myers Squibb Co.
D98: Husten: "Golden Mean of Anticoagulation", Forbes 28 August 2011
D99: Current Drug Targets, 2012, 13, 863-875
D102: Supplementary expert declaration of Prof. Blume, dated 23 January 2018
D129: Journal of Thrombosis and Haemostasis, 2007, 5, 2368-2375
D144: Decision of the District Court of Delaware, USA, dated 5 August 2020
D145: Decision of the Federal Court of Ottawa, Canada, dated 8 January 2021
D146: Affidavit of Prof. Dr. Allan S. Myerson, dated 22 March 2021
D150: The AAPS Journal, 2009, 11(4), 740-746
D151: Expert declaration of Prof. Dr. Henning Blume, dated 21 March 2021
D159/D159A: Expert Report of Professor Frieß, dated 23 August 2021
D160: Expert declaration of Chandra Vema-Varapu, dated 1 December 2021
D162: Lehrbuch der Pharmazeutischen Technologie, Bauer, Kurt H. et al., Stuttgart, Wissenschaftliche Verlagsgesellschaft, 8th ed., 2006, 208-209, 215
D163: Press Release 10 June 2008: "Bristol-Myers Squibb and Pfizer initiate new study in the apixaban Phase 3 clinical trial program"
D164: Expert Opin. Investig. Drugs, (2008) 17(12), 1937- 1945
D165: Expert Report of Dr Stott, 9 February 2022

The opposition division arrived at the following conclusions:

(a) Documents D163-D165 were not admitted into the proceedings.

(b) The main request complied with the requirements of Articles 123(2), 76(1), 83 and 84 EPC.

The subject-matter of the claims of the main request enjoyed the claimed priority. Document D8 could therefore only represent prior art under Article 54(3) EPC. Example 7 of document D8 did not represent prior art.

The claimed subject-matter was new over the prior art.

The claimed subject-matter differed from the closest prior art represented by document D65 in (i) the D_{90} of less than 50 µm for the apixaban particle size, (ii) the crystalline form of the apixaban, (iii) the composition as prepared using a dry granulation process, and (iv) the tablets showing dissolution of at least 77% after 30 minutes.

The objective technical problem was the provision of an improved apixaban tablet, wherein the improvement was the achievement of consistency of exposure. This problem was credibly solved taking also account of document D160. The claimed subject-matter was obvious as solution to this problem in view of the common general knowledge as to the effect of the particle size on the bioavailability

of drugs as well as in view of document D5, which specifically described the preparation of small sized crystalline apixaban in the context of enhancing the bioavailability of sparingly soluble organic compounds.

(c) Auxiliary requests 1-8 did not comply with the requirement of inventive step for essentially the same reasons as explained for the main request. The defined features of a dry granulation process were commonplace.

IV. With their statement of grounds of appeal the patent proprietors maintained the main request and auxiliary requests 1-6, on which the decision under appeal was based.

The following further documents were *inter alia* filed during the appeal proceedings:

A168: ClincalTrials.gov, NCT00536484
(15 September 2009)
A169: ClincalTrials.gov, NCT00220402,
(24 November 2008)
A170: Prescribing Information of Toviaz(R) (February 2011)
A171: Expert Declaration of Prof. Davies, dated 11 July 2022
A172: Decision US Appeal Court of 2021-09-03
A173: Decision CA Federal Court of Appeal of 2022-08-04.
A174: Judgment of the UK High Court, [2022] EWHC 1831 (Pat)
A175: Table of Clinical Trials entries for Controlled Release

Documents A168-A173 were filed by the patent proprietors with the statement of grounds of appeal.

Document A174 was filed by opponents 1, 5, 6 and 9 with their replies to the appeal.

With the reply to the appeal opponent 5 also filed document A175 and resubmitted documents D163-D165 (also identified as A163, A164 and A165).

V. In its communication pursuant to Article 15(1) RPBA of 30 June 2023 the Board expressed *inter alia* the preliminary opinion that

- documents D165 and A168-A175 were to be admitted, whereas documents D163 and D164 were not to be admitted into the appeal proceedings

- the subject-matter of the main request enjoyed the claimed priority and was new over the prior art

- the main request and auxiliary requests 1-6 did not fulfill the requirement of inventive step in view of the reports in documents D65 or D129 on clinical trials involving twice daily administration of tablets with a dose of 5 mg apixaban as closest prior art.

VI. With the letter of 22 December 2023 the patent proprietors responded to the Board's communication.

VII. Oral proceedings were held on 31 January 2024.

VIII. The arguments of the patent proprietors relevant to the present decision are summarized as follows:

(a) Admittance of documents filed during the appeal proceedings

Documents A168-A170 demonstrated with the example of the product Toviaz(R) that contrary to the finding in the decision under appeal reports of clinical trials do not necessarily mention that a tested product is a modified release formulation.

Document A171 was to be admitted, because it addressed statements in documents D159/D159A, which had been admitted by the opposition division and relied upon for the finding on the issue of inventive step following its filing on the final date set for written submissions under Rule 116(1) EPC.

Documents A172 and A173 were to be admitted, because these documents related to the appeal decisions confirming the earlier decisions in documents D144 and D145 by US and CA courts on the issue of inventive step of similar subject-matter as defined in the patent in view of similar evidence.

Document A174 related to a first instance UK decision regarding the patent dealing with the issue of inventive step in view of document D164. Documents D164 and D163 referred to clinical studies involving apixaban, but did not provide any details of apixaban formulations. Document D165 related to a declaration prepared for the UK case and did not represent a response to document A171,

which was of a later date. Documents A174 and D163-D165 were thus not pertinent to the appeal proceedings and should therefore not be admitted.

(b) Main request

The disclosure of clinical trials involving 2.5 or 5 mg apixaban tablets, in particular the Phase 3 trial described in document D65, represented the closest prior art. The claimed subject-matter differed from this prior art in (i) the crystalline form of the apixaban (ii) the D_{90} of less than 50 µm for the apixaban particles, (iii) the tablet comprising a pharmaceutically acceptable diluent or carrier, (iv) the preparation using a dry granulation process, and (v) the tablets showing dissolution of at least 77% of the apixaban after 30 minutes.

The prior art did not reveal that the tablets used in the trials were immediate release (IR) formulations. Contrary to the finding in the decision under appeal the immediate release character of tablets described to be tested in clinical trials could not be assumed by default, which was demonstrated by the example of the product Toviaz(R) in documents D168-D170. Moreover the description of the mere outline of a trial as in document D65 did not disclose the effectiveness of the treatment. The efficacy of the treatment in the trial reported in document D129 did not indicate that the treatment described in document D65 was effective, because the patients in the trials in documents D129 and D65 suffered from different conditions.

As confirmed by document D160 the experimental results reported in the patent indicated that tablets with 77% or higher *in vitro* dissolution of the apixaban in 30 minutes showed consistent solution-like bioavailability. The objective technical problem was therefore the provision of an improved apixaban tablet. References to the bioavailability, consistency of exposure, differences in dissolution rates or efficacy of twice daily administration, would include impermissible pointers to the solution, which was based on the finding that the exposure from 5 mg apixaban tablets is affected by the dissolution rate as first disclosed in the original application for the patent.

As indicated in the declarations in documents D96, D102 and D151 by Prof. Blume the skilled person had motivation to seek enhanced dissolution of apixaban in a tablet containing only 5 mg apixaban. At a dose of 5 mg apixaban qualified according to the Biopharmaceutical Classification System (BCS) as a class III compound, which implied that its bioavailability was not expected to depend on its dissolution, but only on its absorption. As explained in the declaration by Prof. Davies in document A171 any reservations in the context of the BCS as to the dissolution rates of class III drugs did not concern the skilled person's expectations in the original development of an IR tablet, but addressed the eligibility for waivers for *in vivo* bioavailability and bioequivalence studies, the so-called "biowaivers", for subsequent market authorizations.

The combination of the features of the defined tablet contributed to the solution of the objective technical problem. The patent underlined the relevance of the preparation of the particles using a dry granulation process in paragraphs [0012] and [0034], which indicated that the preparation using a dry granulation process resulted in tablets with higher apixaban exposure and faster apixaban dissolution as compared to tablets prepared by a wet granulation process. Document D121 confirmed that tablets made using the dry granulation process have more consistent dissolution rates. As indicated by document D28, wet granulation was the most widely used and most general method of tablet preparation. The prior art provided no suggestion towards the preparation by dry granulation for solving the objective technical problem.

As indicated by the declaration by Prof. Myerson in document D146 and by Prof. Davies in document A171 the skilled person was also well aware of the disadvantages of a reduced particle size of active ingredients and the availability of alternatives measures for enhancing the dissolution rate. The skilled person would therefore not seek to improve the tablets of the prior art by using crystalline apixaban with a reduced particle size, especially if the prior art provided no motivation for the reduced particle size.

Document D5 described a process for transforming a first polymorph of a chemical agent into a second polymorph of the same agent involving a particular apparatus and specific process steps. Document D5 presented examples of this process involving apixaban. Faced with the objective technical

problem the skilled person had no motivation to consider the teaching of document D5, which did not refer to any particular dose of apixaban in a pharmaceutical formulation and was therefore of no relevance to the claimed subject-matter which involved a tablet comprising a dose of apixaban at which its bioavailability could not be expected to be influenced by its dissolution.

Documents D97-D99 demonstrated that the claims covered a successful pharmaceutical product, namely Eliquis(R), which represented a secondary indication that the claimed subject-matter involved an inventive step.

(c) Auxiliary requests

Auxiliary requests 1-3 complied with the requirement of inventive step for the same reasons as the main request.

Auxiliary requests 4 and 5 additionally defined the composition comprising 5 mg crystalline apixaban for use in the treatment of a thromboembolic disorder. The effective treatment implied by this feature further distinguished the claimed subject-matter from the tablets used in the trial of document D65, for which no efficacy was reported. Document D129 recommended a total daily apixaban dose of 5 mg for Phase III evaluation, preferably in a 2.5 mg twice daily regimen, and thereby tought away from the claimed tablets comprising 5 mg apixaban and their twice daily administration.

Auxiliary request 6 additionally defined the apixaban particles to have a D_{90} of less than 25 µm

as measured by laser light scattering. Such particles had not been disclosed or suggested in the prior art.

IX. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of documents filed during the appeal proceedings

Document D165 was resubmitted in response to the filing of document A171. Document A174 related to the decision from the UK High Court denying that the patent involved an inventive step in view of document D164. Document A174 provided a relevant opinion regarding the common knowledge which was in agreement with the declaration in document D165. Documents D164, D165 and A174 should therefore be admitted.

Documents A168-A171 were not to be admitted for being late filed without justification and lacking relevance. Documents A172 and A173 lacked relevance, because they concerned, like documents D144 and D145, decisions from jurisdictions which do not apply the EPC and EPO case law and did not provide further information relevant to the appeal proceedings.

Document A175 was filed in response to the filing of documents A168-A170 by the patent proprietors and presented a list of clinical trials, wherein drugs in a modified release form are explicitly identified.

(b) Main request

Document D8 disclosed in example 7 an IR tablet comprising 5 mg apixaban which anticipated the claimed subject-matter. The pharmacokinetic data disclosed in Table 1 on page 65 of document D8 for this tablet corresponded to the data in Table 6 of the patent for tablets according to the claimed invention, which indicated that the tablet of example 7 of document D8 was covered by claim 1 of the main request.

The disclosure of clinical trials involving 2.5 or 5 mg apixaban tablets for twice daily administration, including the Phase 3 trial described in document D65 as well as the Phase 2 trial described in document D129, represented the closest prior art. The low doses of 2.5 and 5 mg implied the presence of a diluent or carrier. The twice daily administration and the lacking reference to any modified release of the apixaban indicated that the tablets were conventional formulations for immediate release. The preparation by dry granulation did not further distinguish the claimed tablets. Document D65 implied that apixaban was bioavailable from twice daily administration of the tablets and document D129 explicitly mentioned the therapeutic efficacy from administration of the twice daily dose of 5 mg together with the pharmacokinetic profile of apixaban indicating its suitability for twice daily administration.

The available experimental results did not demonstrate any effect over the tablets of the prior art. Moreover, the defined dissolution at pH 6.8 did not exclude longer dissolution times of the

defined tablet at the lower pH in the stomach, for instance due to an enteric coating of the tablets. The problem to be solved would therefore merely concern the provision of an alternative tablet or the provision of further information with respect to the tablets used in the trials of the prior art.

In as far as the available results were nevertheless considered to demonstrate that the claimed formulation was associated with the effect of consistent solution-like bioavailability of the apixaban and the objective technical problem could be formulated as the provision of a an optimized tablet suitable for effective twice daily administration of apixaban, the claimed solution did not involve an inventive step.

In as far as the twice daily administration of the known tablets did not already imply that these tablets were immediate release formulations, the skilled person would recognize that the twice daily dosage regimen was consistent with the immediate release of the apixaban from the tablets.

The reduction of the particle size of active ingredients was an established method for improving dissolution characteristics and thereby the bioavailability of active agents in IR formulations. This common general knowledge was reflected in document D5, which described the preparation of crystalline apixaban with a reduced particle size.

The preparation of tablets using a dry granulation process was well known in the art. In as far as the preparation of the tablets involving a dry

granulation process represented a distinguishing feature of the defined tablets, no effect of this feature on the performance of the tablets had been demonstrated to support an inventive step.

As explained in the declaration by Prof. Frieß in document D159/159A and the declaration by Dr Stott in document D165, the expectation that the bioavailability of a BSC class III drug depends on its absorption rate and not on its solubility was subject to the reservation that the drug has an adequate dissolution rate. This reservation did not exclusively concern the eligibility of generic drugs for biowaivers for subsequent market authorizations.

The skilled person who intended to optimize the tablets of the prior art would therefore in view of the teaching of document D5 or even just the common general knowledge by itself provide apixaban in a crystalline form with a reduced particle size and secure its rapid dissolution and thereby arrive at the claimed solution in an obvious manner.

Known potential disadvantages of particle size reduction were not addressed in the patent and could not withhold the skilled person from applying this well established method to optimize the dissolution characteristics of crystalline apixaban.

(c) Auxiliary requests

The trials described in the prior art involved tablets for administration of an oral dose of 5 mg apixaban. The definition of the amount of apixaban

in auxiliary requests 1-3 did therefore not represent any additional distinguishing feature that could support an inventive step.

The trials of the prior art already included the twice daily administration of tablets with a dose of 5 mg apixaban, which in line with document D65 resulted in bioavailability of the apixaban and according to document D129 allowed for effective treatment. The definition of the use in treatment of thromboembolic disorders and of the twice daily administration in auxiliary requests 4 and 5 could therefore also not support an inventive step.

Auxiliary request 6 additionally defined the particles to have a D_{90} of less than 25 µm as measured by laser light scattering. No unexpected effect had been shown to be associated with this particular low D_{90}. Moreover, document D5 already described the preparation of crystalline apixaban having a particle size of less than 20 µm. The subject-matter of auxiliary request 6 did therefore also not involve an inventive step.

X. The patent proprietors (appellants) requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or one of auxiliary requests 1-6, originally filed as auxiliary requests 2-8 on 24 March 2021.

The patent proprietors further requested that documents A168-A173 be admitted and documents D163-D165, A174 and A175 not be admitted into the appeal proceedings.

XI. The opponents (respondents) requested that the appeal be dismissed.

The opponents further requested that documents D163-D165 and A174 be admitted and that documents A168-A173 not be admitted into the appeal proceedings.

Reasons for the Decision

Admittance of documents and submissions filed during the appeal proceedings

1. In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that documents D165 and A168-A175 were to be admitted and that documents D163 and D164 were not to be admitted into the appeal proceedings.

No substantive arguments regarding the admittance of these documents were subsequently presented by the parties.

The Board has therefore confirmed its preliminary opinion and has admitted documents D165 and A168-A175 and not admitted documents D163 and D164 into the appeal proceedings.

Main request

2. Priority / Novelty

In its communication pursuant to Article 15(1) RPBA the Board further expressed the preliminary opinion that the Board agreed with the finding in the decision under appeal that the priority is valid for the main request, that document D8 did not represent prior art under

Article 54(2) EPC, and that the subject-matter of the main request was new over the prior art.

No substantive arguments regarding the validity of the claimed priority and the novelty of subject-matter of the main request were subsequently presented by the parties.

The Board has therefore confirmed its preliminary opinion to conclude that the subject-matter of the main request enjoys the claimed priority and that this subject-matter is novel over D8.

3. Inventive step

3.1 Closest prior art

Document D65 announces a placebo controlled double blind Phase 3 clinical trial to evaluate the efficacy and safety of twice daily administration of an 2.5 or 5.0 mg dose of apixaban in the form of tablets for the treatment of patients with deep vein thrombosis or pulmonary embolism.

Document D129 describes a Phase 2 clinical trial investigating the efficacy and safety of doses of 5, 10 or 20 mg of apixaban per day by once or twice daily administration of apixaban tablets for thromboprophylaxis in patients following total knee replacement. Document D129 reports efficacy for all doses with a dose-related increase in the incidence of bleeding events (see D129, abstract). Document D129 further mentions that apixaban reaches peak levels after 3 hours in healthy volunteers and that with a half-life of 12 hours apixaban has a pharmacokinetic

profile compatible with twice or possibly once daily administration (see D129, page 2369, left column).

It was not in dispute that the disclosure of clinical trials involving tablets for twice daily administration of an oral dose of 2.5 or 5. mg, including the Phase 3 trial described in document D65 as well as the Phase 2 trial described in document D129, qualify as suitable starting points in the prior art.

The Board considers that the definition of the mere presence of a pharmaceutically acceptable diluent or carrier does not represent a distinguishing feature of the tablet defined in claim 1 of the main request with respect to the tablets used in the trials described in documents D65 and D129, because in view of the low amounts of 2.5 or 5 mg of apixaban the presence of such excipients is technically required and thus implicit for the tablets described in the prior art.

On the other hand, the Board observes that the defined preparation by a dry granulation process may be expected to result in a characteristic internal structure of the resulting tablets.

The Board is further not convinced that the suitability of the tablets used in the trials for twice daily administration and the absence of any reference to a particular release profile necessarily mean that these tablets were conventional immediate release (IR) formulations.

The Board therefore considers that the claimed subject-matter differs from the closest prior art in

- the crystalline form of the apixaban,

- the D_{90} of less than 50 µm for the apixaban particles,

- the preparation using a dry granulation process, and

- the tablets showing dissolution of at least 77% of the apixaban after 30 minutes.

3.2 Objective technical problem

The patent presents in paragraphs [0036] and [0037] a discussion of the experiments for which the results are presented in Tables 6 and 6a and Figures 1-4. In this discussion the patent informs that based on the results of the described experiments solution-like bioavailability may be expected statistically with 90% confidence for tablets with a dissolution rate of at least 77% in 30 minutes and that such dissolution may already be achieved with tablets containing 5 mg apixaban with a D_{90} below 89 µm. The explanations in documents D93 and D160 confirm this information. The claimed tablets comprising up to 5 mg apixaban with the defined dissolution profile and an even lower D_{90} of less than 50 µm may therefore be considered to also allow for solution-like bioavailability of the tablet. This effect derives from the identified distinguishing features of the tablet and may therefore according to the Board not be ignored merely because the claim does not exclude features that could obstruct the realisation of the effect, such as an enteric coating that could prevent the dissolution of the tablet in the stomach and thereby the solution-like bioavailability of the tablet.

A direct comparison with the tablets of the trials in documents D65 or D129 is precluded due to the absence of definitive information in documents D65 and D129 regarding the solid state form, the dissolution profile and the particle size of the apixaban in the tablets used in the trials. However, in view of the absence of this information regarding the exact constitution of the tablets of the prior art the Board considers that taking account of the above mentioned solution-like bioavailability of the claimed tablets the objective technical problem may still be seen in the provision of an optimized tablet suitable for effective twice daily administration of apixaban.

In this context the Board rejects the suggestion by the patent proprietors that this formulation of the objective technical problem includes an impermissible pointer to the solution by anticipating that the optimized tablet is a tablet for the effective twice daily administration of apixaban. Pointers to the solution implied by the differences with the starting point in the prior art, in particular the dissolution profile of the apixaban in the tablet, are indeed to be avoided in the formulation of the objective technical problem. However the objective of providing an optimized tablet for effective twice daily administration of apixaban does not include any pointer to a difference with the starting point in the prior art, because document D129 already discloses such a tablet for effective twice daily administration of apixaban and because the trial announced in document D65 was at least aimed at evaluating the efficacy of the described tablets.

Starting from the tablets as described in documents D65 or D129 the Board therefore considers the provision of

an optimized tablet suitable for effective twice daily administration of apixaban as a realistic formulation of the objective technical problem which avoids any pointer to the claimed solution.

3.3 Assessment of the solution

3.3.1 The prior art describes the tablets used in the trials as suitable for twice daily administration (see D65 under "Intervention", see also D129, abstract) and refers to the compatibility of the pharmacokinetic profile of apixaban with such dosing regimen (see D129 page 2369, left column, lines 2-6). Whilst this information may not warrant the definitive conclusion that the tablets used in the clinical trials were immediate release formulations, the skilled person would recognize that an immediate release profile fits with the dosage regimen for the tablets used in the trials described in the prior art. The skilled person would therefore be motivated to develop optimized immediate release tablets comprising up to 5 mg apixaban as solution to the above formulated objective technical problem.

In this context the skilled person would on the basis of his common general knowledge (see for instance D135) be aware of the Biopharmaceutical Classification System (BCS). The BSC categorises drugs in four classes according to their dose weighted water solubility and membrane permeability, which broadly allows the prediction of the rate-limiting step for absorption following oral administration and the effect of the formulation of a drug on its oral bioavailability. The BSC is used in the context of drug discovery and development as well as in drug approval procedures (see D150, abstract and page 740, right column).

A compound with a high water solubility in relation to its dose strength and a low membrane permeability is categorized as a BSC class III drug. For BSC class III drugs the permeability is generally predicted as the rate-limiting factor in absorption rather than dosage form factors which affect the dissolution (see D150, page 741, right hand column).

In view of the solubility of apixaban of 40 µg/ml at relevant conditions reported in the patent (paragraph [0005], see also D32, pdf-page 17) apixaban may qualify at a dose of 5 mg as such a BCS class III drug. According to the patent proprietors the skilled person would therefore not have expected that the dissolution rate of apixaban, as a BCS class III drug, would have affected its absorption and would thus not have considered measures aimed at increasing apixaban's dissolution rate in order to optimize tablets for twice daily administration of apixaban as described in documents D65 or D129.

However, the literature cited in the appeal proceedings regarding predictions for oral bioavailability based on the BCS, in particular BCS class III drugs, consistently maintains a reservation with respect to the sufficiently rapid dissolution rate of the drug concerned, namely that the permeability of the active pharmaceutical ingredient is expected to be the rate controlling step of the absorption only if the dosage form dissolves rapidly:

> see document D75, page 923, left column: "If the dissolution of Class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in*

vivo."; see also page 923, right column: "To minimize the possibility of dissolution behaviour anomalies (...) it would be necessary to set a more rapid *in vitro* dissolution rate criterion of no less than 85% within 15 min for Class III drugs"

see document D74, page 119, right column: "If their dissolution is rapid under all physiological pH conditions, it can be expected that they will also behave like an oral solution *in vivo*"; see also page 118, right column: "Consequently, additional requirements on dissolution behaviour were introduced in the system. Thus, a waiver of bioavailability studies may only be granted for products whereby more than 85% of the drug ingredient is dissolved in 30 min in all physiological media."

see document D9, page 417, right column: "if dissolution is fast, i.e. 85% dissolved in less than 15 min. this variation will be due to gastrointestinal transit (...) rather than dosage form factors"

see document D88, page 2 :"In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool (...)"; see also pages 2-3, bridging sentence: "an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes (...)"

see document D40, page 1243, right column: "Therefore, biowaivers for BCS class 3 drug

products with suitably rapid dissolution..."; see also page 1236, right column: "both the WHO and the EMA extend biowaivers to some class III drug compounds when they meet the criterion for very rapid dissolution drugs (>85% solubility at pH 1,2-6.8 in 15 min)"

see document D72, page 25/27: "BCS-based biowaver are also applicable for an immediate release drug product if the drug has (...) very rapid (85% within 15 minutes *in vitro)* dissolution (...)"

see document D26, page 3, lines 2-5: "The BCS suggests that for (...) (case 3) drugs, 85% dissolution in 0.1 N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution."

see document D81, page 307, right column: "For Class III compounds that are rapidly dissolving (...) a new formulation may be considered acceptable if both the new and old formulations are more than 85% dissolved in 15 min (...)"

see document D82, page 1380, left column: "a more rapid dissolution requirement of at least 85% dissolved in 15 min is an important requirement in order to extend biowaivers to Class 3 drugs."

see document D150, page 741, right column: "An IR product is characterized as rapidly dissolved if not less than 85% of the labeled drug amount is dissolved within 30 min" and "If the *in vitro* dissolution of Class III drug is rapid under all physiological pH conditions, its *in vivo* behaviour will essentially be similar to oral solution (...)"

see document D162, page 209, right column: "Unter der Annahme, dass insbesondere (...) die Löslichkeit und die Fähigkeit, die Intestinalmembranen zu permeieren, für die Bioverfügbarkeit entscheidend sind, wurde as Biopharmazeutische Klassifizierungssystem (...) entwickelt" [translation by the Board: "Assuming that in particular (...) the solubility and the ability to permeate the intestinal membranes are crucial for bioavailability, the Biopharmaceutical Classification System (...) was developed"]; see also page 215, right column: "Daher ist die Bestimmung der Lösungsgeschwindigkeit eins der wichtigsten Bestimmungsverfahren im Rahmen der Qualitätskontrolle" [translation by the Board: "Therefore, the determination of the dissolution rate is one of the most important determination procedures in the context of quality control"]

This reservation is further in line with the common general knowledge that the particle size of a drug may affect its bioavailability, if the drug's absorption is limited by its dissolution rate (see D80, page 2703, left column; D48, page 335; D25, page 11; D38, page 5; D61, page 288, left column).

Notably, the above cited passages from the literature concerning predictions for oral bioavailability of BCS class III drugs qualify the dissolution of a drug as rapid, if at least 85% of the drug dissolves within 30 minutes or even more stringently within 15 minutes. At the same time these passages underline the importance of such rapid dissolution for the assumption that a composition with such a rapidly dissolving drug will behave *in vivo* essentially similar to an oral solution

or the assumption that different formulations of a drug will show bioequivalence. Such assumptions are not only relevant for granting "biowaivers", which represent permission to proceed with clinical studies for obtaining regulatory approval using different formulations without showing bioequivalence of the formulations on the basis of *in vivo* studies (see document A171, page 5, lines 6-10), but also in the original development of drug formulations, because solution-like in vivo behaviour corresponds to the optimal performance of an immediate release formulation.

The Board therefore considers that in addressing the problem of providing an optimized tablet suitable for twice daily administration of apixaban the skilled person would take up measures to secure the rapid apixaban dissolution and in particular aim for a dissolution of 85% within at least 30 minutes.

In this context the Board observes that the conditions for the dissolution test defined in claim 1 of the main request largely correspond to conventional conditions for establishing the rate of dissolution of a drug (compare for instance document D150, page 741, right hand column). As no particular effect on the performance of the defined tablet has been demonstrated to be associated with the defined testing conditions, the Board does not consider that the definition of these conditions contribute to an inventive step.

3.3.2 It was not in dispute that the reduction of the particle size of pharmaceutically active agents was a well established method for improving the dissolution characteristics of the active agents.

Document D5 refers to this common general knowledge stating that the bioavailability of a sparingly soluble organic compound is often enhanced when the agent is in pure from and has a small and uniform particle size with a high surface area and short dissolution time (see D5, paragraph [0003]). In this context document D5 recognizes the need for a robust crystallization process for providing small and uniform crystals with high purity, stability and surface area without the necessity of post-crystallisation milling (see D5, paragraph [0011]). To address this need document D5 discloses a process for transforming a polymorph form with large crystals in a polymorph form with small crystals (see D5, paragraphs [0012] and [0020]). Document D5 presents examples of the disclosed process involving apixaban in which large needle-shaped crystals are transformed into small, granular crystals having a D_{90} particle size of less than 20 µm (see D5, Examples 1-3).

In view of the described purpose of the process in document D5, namely the provision of crystals of a small uniform particle size with high purity, high stability and high surface area, which in line with the mentioned common general knowledge results in an enhanced dissolution rate, the skilled person who intends to prepare an optimized tablet for twice daily administration of apixaban by securing at 85% apixaban dissolution within at least 30 minutes, would take account of the teaching document D5 and use the crystalline apixaban having a particle size D_{90} of less than 20 µm as described in the examples of document D5.

In this context the Board observes that the preparation of tablets by a dry granulation method was a well known and available option. In the absence of any unexpected

effect from the defined preparation of the claimed tablets by a dry granulation process, the defined preparation does not contribute to an inventive step.

Accordingly, the provision of tablets comprising up to 5 mg crystalline apixaban particles having a D90 less than 50 µm prepared by a dry granulation process and having a dissolution profile as defined in claim 1 of the main request would seem obvious to the skilled person as solution to the mentioned objective technical problem.

3.3.3 The patent proprietors referred to the relevance of the preparation of the particles using a dry granulation process indicated in paragraphs [0012] and [0034] of the patent and the confirmation in document D121 that tablets made using the dry granulation process have more consistent dissolution rates to argue that the dry granulation process, which was not the most widely used and most general method of tablet preparation (see D29, page 1641, right column), unexpectedly contributed to the performance of the claimed tablets.

However, the Board observes that in paragraph [0012] the patent states:

"formulations made using a wet granulation process resulted in lower exposures compared to the exposures obtained from a dry granulation process."

From this statement, which does not further specify the prepared tablets, it is not evident that the compared tablets essentially differed only in their preparation using a dry versus wet granulation method and not in other features that could affect the exposures from the tablets, such as solubilizing excipients.

In fact, the patent subsequently refers in paragraph [0034] to results in Tables 5 and 5a, which would indicate that having a dry granulation process will result in faster dissolution compared to that from a wet granulation process. However, the tablets from the dry granulation method used for the comparison in Tables 5 and 5a comprised an amount of 1% of the surfactant sodium lauryl sulfate, which was not present in the tablets from the wet granulation method (see the patent, Tables 3 and 4) and which may well have affected the observed dissolution rates.

Document D121, which presents the Assessment report for Eliquis by the European Medicines Agency, contains the following observation:

"Development work included the evaluation of the different types of granulation and the use of a film coat for the tablets. It was found that tablets made using the dry granulation process have more consistent dissolution rates."

This observation indicates that a particular dry granulation process ("the dry granulation process") resulted in tablets with more consistent dissolution rates with respect to tablets from other types of granulation, but does not support the conclusion that dry granulation will in general result in more consistent dissolution rates.

Accordingly, neither paragraphs [0012] and [0034] of the patent nor the cited statement in document D121 substantiate any unexpected effect from the defined preparation of the claimed tablets by a dry granulation process.

3.3.4 The patent proprietors' argument relying on the declarations in documents documents D96, D102, D151 and A171 that the enhanced dissolution of apixaban from a formulation with a 5 mg dose was not expected to have any effect on the bioavailability of the apixaban, because at such dose the apixaban is to be regarded as a BCS class III drug is also not considered convincing.

As explained in section 3.3.1 above, the expectations concerning the bioavailability of a 5 mg dose of apixaban as a BCS class III drug are subject to the reservation that the dissolution rate of the drug is sufficiently rapid.

In contrast to the declarations in documents D159/A159A and A165 relied upon by the opponents the declarations in documents D96, D102, D151 and A171 relied upon by the patent proprietors do not seem to take due account of this reservation.

3.3.5 The patent proprietors further argued, that the skilled person would not consider the teaching of D5 for solving the objective technical problem starting from the tables used in the clinical trials of documents D65 and D129, because document D5 did not mention any particular dose of apixaban in a pharmaceutical formulation and was therefore of no relevance to the claimed subject-matter which involved a tablet comprising a dose of apixaban at which it qualified as a BCS class III drug.

This argument is not convincing, because it fails to acknowledge that document D5 describes a process for preparing apixaban having a small uniform particle size with high purity, high stability and high surface area,

which in accordance with the common general knowledge specifically cited in document D5 may be expected to allow for enhanced bioavailability.

3.3.6 The patent proprietors' further argument, that the skilled person would in view of the potential disadvantages of a reduced particle size of active ingredients and the availability of alternatives for enhancing the dissolution rate not seek to develop an IR tablet comprising crystalline apixaban with a reduced particle size, is also not considered convincing.

The argument regarding the disadvantages of a reduced particle size had been rejected in the decision under appeal (see section 13.2.3.3.4), because the skilled person would tolerate known potential disadvantages of a feature, if the interest in the advantage of the feature prevails, and because it had not been indicated how the claimed compositions would overcome the alleged disadvantages. Taking account of the common general knowledge regarding particle size reduction as a conventional method to achieve *inter alia* enhanced dissolution of drugs as well as the actual availability of apixaban having a small uniform particle size with high purity, high stability and high surface area from the process described in document D5 the Board agrees with the finding in the decision under appeal.

The Board further considers that the availability of alternative methods for improving the dissolution rate of apixaban does not distract the skilled person from applying the conventional method of particle size reduction to enhance the dissolution of apixaban from a tablet for twice daily administration.

3.3.7 According to the decision under appeal (see section 13.2.3.3.6) the evidence regarding the success of the product Eliquis(R) as reported in documents D97-D99 did not allow for the conclusion that this success was due to the distinguishing features of the claimed subject-matter with respect to the closest prior art. The Board agrees and therefore considers that the success of the product Eliquis(R) does not affect the finding that the claimed subject-matter lacks an inventive step.

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

Auxiliary requests

4. Auxiliary requests 1-3 (inventive step)

In auxiliary requests 1-3 the amount of apixaban in the tablet is defined more restrictively than in the main request. However, the amount of apixaban defined in auxiliary requests 1-3 still includes 5 mg, which corresponds to the oral dose described in documents D65 and D129. Auxiliary requests 1-3 do thus not define any relevant additional distinguishing feature with respect to the closest prior art and therefore do not meet the requirement of inventive step for the same reasons as set out for the main request.

5. Auxiliary requests 4-5 (inventive step)

Document D129 already reported the efficacy of apixaban administered in the form of tablets in a twice daily oral dose of 5 mg. The additional features in auxiliary requests 4 that the tablet is for use in the treatment of a thromboembolic disorder and in auxiliary request 5

that this use involves twice daily oral administration thus correspond with the known indication for the oral 5 mg dose of apixaban and its twice daily administration. These features do thus not relate to any effective technical contribution over the prior art. Auxiliary requests 4-5 do therefore also not meet the requirement of inventive step.

6. Auxiliary request 6 (inventive step)

Claim 1 of auxiliary request 6 additionally more specifically defines the apixaban particles to have a D_{90} of less than 25 µm. The Board observes that document D5 already describes the availability of crystalline apixaban having a particle size of less than 20 µm. As the patent proprietors have not relied on any unexpected effect related to the particles having a D_{90} of less than 25 µm the Board therefore concludes that the subject-matter of claim 1 of auxiliary request 6 also lacks an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated