Internal distribution code:

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

Datasheet for the decision of 6 February 2024

Case Number: T 1188/22 - 3.3.07

Application Number: 18718476.7

Publication Number: 3416627

IPC: A61K9/20, A61K31/437

Language of the proceedings: EN

Title of invention:
ORAL DOSAGE FORM COMPRISING RIFAXIMIN IN FORM BETA

Patent Proprietor:
Sandoz AG

Opponent:
Alfasigma S.p.A.

Headword:
ORAL DOSAGE FORM COMPRISING RIFAXIMIN IN FORM BETA/Sandoz AG

Relevant legal provisions:
RPBA 2020 Art. 13(1)
EPC Art. 83, 56

This datasheet is not part of the Decision
It can be changed at any time and without notice

Keyword:
Admission of a document (Yes)
Main request - Sufficiency of disclosure (Yes)
Main request - Inventive step (No)

Decisions cited:

Catchword:

This datasheet is not part of the Decisior
It can be changed at any time and without notic

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 1188/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 6 February 2024

Appellant: (Opponent)	Alfasigma S.p.A. Via Ragazzi del '99 n. 5 40133 Bologna (IT)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Patent Proprietor)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 May 2022 concerning maintenance of the European Patent No. 3416627 in amended form.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European Patent 3 416 627 had been opposed under Article 100 (a), (b), (c) EPC on the grounds that its subject-matter lacked inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

II. The appeal lies from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on the main request filed with letter of 4 February 2021.

Claim 1 of the main request read:

"1. Tablet for delayed release comprising:
(A) rifaximin in polymorphic form β, and
(B) one or more pharmaceutical excipient(s)
wherein the rifaximin (A) contains 700-900 rifaximin mg calculated on the basis of anhydrous rifaximin, and
wherein the tablet is substantially free of enteric release material".

III. The documents cited during the opposition proceedings included the following:

D1: USP-NF, item 711, Dissolution, https://online.uspnf.com/uspnf, official as of 1 May 2016
D2: Experimental Report, of July 30, 2020, by Dott. Fabrizio Giorgi
D3: European Medicines Agency, Guideline on quality of oral modified products, 20 March 2014, pp.1-16 release
D5: EP 1 676 847 B1
D6: WO 2006/094737 A2

D7: EP 2 618 819 B1
D12: EP 2 011 486 A1
D18: EMA Reflection paper on the dissolution specification for Generic solid oral immediate release products with systemic action, 2017
D20: Rutgeerts et al, Controlled trial of Metronidazole Treatment for Prevention of Crohn's recurrence after Ileal Resection, Gastroenterology, 1995, 108:1617-1621
D21: Di Febo et al, New trends in non-absorbable antibiotics in gastrointestinal disease, Ital. J. Gastroenterol., 1992, Nov-Dec; 24(9 Suppl.2), 10-3
D22: Prantera et al., Antibiotic Treatment of Crohn’s disease; results of multicenter, double blind, randomized, placebo-controlled trial with rifaximin, Aliment. Pharmacol. Ther., 23, 1117-1125 (2006)

IV. According to the decision under appeal, the claimed invention was sufficiently disclosed.

D20 and D21 were not admitted, since late filed and *prima facie* not more relevant than the documents on file. D22 was admitted in view of its relevance for the assessment of inventive step.

D12 was considered to represent the closest prior art, rather than D5 or D6; D12 did not disclose the claimed polymorphic form of rifaximin and the content of 700 to 900 mg of rifaximin. The technical problem was the provision of a high strength tablet formulation of rifaximin suitable for the treatment of Crohn's disease by once daily administration. The claimed solution was not obvious in view of D6, D7 and D22.

V. The opponent (hereinafter the appellant) filed an appeal against said decision.

VI. In its reply to the grounds of appeal dated 5 January 2023, the patent-proprietor (herein after the respondent) filed auxiliary requests I to XXXI.

VII. With a letter dated 12 April 2023, the appellant filed a new evidence:

D23: Excerpt of the 4th edition of the European Pharmacopoeia

VIII. A communication from the Board, dated 31 October 2023, was sent to the parties.

IX. Oral proceedings took place on 6 February 2024. During the oral proceedings the respondent withdrew all auxiliary requests I-XXXI.

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

Admission of D20 and D21 into the proceedings

D20 and D21 were filed as a direct reaction to respondent's submissions made during the opposition proceedings, wherein it was pointed out that the surprising technical effect of the tablet of the invention was that an improved pharmaceutical composition comprising rifaximin β being suitable for treating Crohn’s disease could be obtained. The objective technical problem in view of both D5 and D6 as starting points had then been formulated as the provision of an improved pharmaceutical composition comprising rifaximin for use in treating Crohn’s disease.

Admission of D23 into the proceedings

This document was filed in reaction to the decision of the opposition division and to some arguments of the respondent regarding D3. It gave a further definition of immediate and delayed release dosage forms.

Main request - Sufficiency of disclosure

According to the appellant, the claimed dosage form could not constitute a delayed release dosage form, in particular in view of the definitions given in D3 or D23 and in the absence of any excipient in the claimed composition or in the examples of the patent which could involve such release. In Figure 4 of the patent, the delayed release was due to the slow dissolution properties of rifaximin in the first acidic medium and the presence of sodium lauryl sulfate (SLS) in the second alkaline dissolution medium. This was demonstrated in D2.

Main request - Inventive step

D12 was the closest prior art. The distinguishing features were the polymorphic form of rifaximin and the tablet content of 700-900 mg. In the absence of any effect linked with these differences, the problem was the provision of an alternative tablet comprising rifaximin that does not comprise an enteric material. The solution was obvious in view of D12, but also D6 and D7.

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

Admission of D20 and D21 into the proceedings

The decision of the opposition division was correct, since more relevant documents than D20 or D21 were already on file.

Admission of D23 into the proceedings

This document was late-filed and should have been filed with the grounds of appeal. D3 was discussed during the opposition proceedings and there was no justification of such late-filing in response to D3.

Main request - Sufficiency of disclosure

The definition of "delayed release" could not be limited to gastroresistant forms and to the disclosure of D23 or D3. D18 gave for instance a different definition of "immediate release" than D3. The examples of the patent showed a clear delayed release profile through a test also used in D6.

Main request - Inventive step

D12 was the closest prior art. The technical effect of the polymorphic form of rifaximin was a reduced dissolution, which made the dosage form more convenient for the treatment of Crohn's disease. The high content allowed the tablet to be easier to administer and to improve the patient's compliance.The problem was the provision of a high strength tablet of rifaximin suitable for treating Crohn's disease which can be administered once-a-day. There was no motivation in D12

to prepare tablets with a content of 700-900 mg. The same applied to D6 and D7. The claimed solution could not be inventive.

XII. Requests

The appellant requested that the decision under appeal be set aside and the patent be revoked. The appellant also requested that documents D20 and D21 be admitted into the appeal proceedings.

The respondent requested that the appeal be dismissed. The respondent also requested that documents D20, D21 and D23 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admission of D20 and D21 into the appeal proceedings

1.1 These documents were filed by the appellant during the opposition proceedings, with its letter dated 7 January 2022 on the final date for making written submissions under Rule 116 EPC. The oral proceedings took place on 8 March 2022.

The opposition division considered that the documents were late-filed and *prima facie* not relevant, and for this reason would only unnecessarily complicate the proceedings (Article 114(2) EPC). As a consequence, they were not admitted.

1.2 D20 discloses that metronidazole, i.e. a drug different from rifaximin which is the active ingredient of the composition of claim 1, is useful to treat Crohn's disease.

D21 is an abstract which cites rifaximin and its possible use in the treatment of Crohn's disease.

1.3 In view of their content, the Board agrees with the opposition division that the disclosure of D20 and D21 remains very remote from the claimed subject-matter, in particular in comparison to some documents already on file. Furthermore, during the opposition proceedings, D22 was already admitted since relating to rifaximin gastroresistant granules in the treatment of Crohn's disease.

Consequently, the Board does not see any reason to overrule the opposition division's conclusion that D20 and D21 are not *prima facie* relevant for the discussion on inventive step.

1.4 A Board should only overrule the way in which an opposition division has exercised its discretion if it comes to the conclusion that the opposition division used the wrong principles, failed to take into account the right principles, or exercised its discretion in an unreasonable or arbitrary manner.

In the present case, the opposition division has exercised its discretion reasonably and according to the right criteria. During the oral proceedings before the opposition division, both parties had presented their arguments on the content and admissibility of the documents, as shown by the minutes and the decision of the opposition division.

The opposition division had based its ruling on the principle of *prima facie* relevance, which is a decisive principle for deciding on the admittance of late filed

documents. Consequently, there is no justification to overturn the opposition division's discretionary decision and to admit D20 and D21 into the proceedings.

2. Admission of D23 into the appeal proceedings

2.1 D23 was filed by the appellant after the respondent replied to the statement of grounds of appeal. The document is an excerpt of the 4th edition of the European Pharmacopoeia and gives several definitions, *inter alia* the definition of delayed release compositions, namely under "Darreichungsformen mit verzögerter Wirkstoffreisetzung", that "dosage forms with delayed release of active ingredients are preparations with modified release of active ingredients in which the release of active ingredients is not immediate".

2.2 The Board considers that this document was filed in response to an argument of the respondent with regard to D3 and the discussion on the term "for delayed release" in claim 1 and its interpretation, which might have an incidence in particular on the discussion on sufficiency of disclosure. The content of this document belongs to common general knowledge and relates to issues raised during the opposition and appeal proceedings without giving rise to new issues.

Consequently, the Board decides to admit document D23 into the appeal proceedings (Article 13(1) RPBA).

3. Main request - Sufficiency of disclosure

3.1 The term "tablet for delayed release" has been objected by the appellant as not sufficiently disclosed by the contested patent. According to the appellant, the term

has been construed by the respondent to allow for more than one interpretation, while this term has an acknowledged meaning in the art. The appellant cites in particular D2 and D3 in support of its objection.

3.2 Claim 1 of the main request relates to a "tablet for delayed release" which has the particularity that "the tablet is substantially free of enteric material".

The claimed invention relates in particular to a dosage form comprising rifaximin in a form not substantially soluble in the acidic medium of the stomach, this form being the specific polymorphic form β of rifaximin (see the specification, par. [0006]-[0008]). The dosage form releases less than 10% of rifaximin until having passed the stomach or within 120 minutes (cf. the specification, par. [0015]-[0018]).

Figure 4 of the patent shows that a tablet as claimed has a delayed dissolution profile close to a tablet made with enteric material. The dissolution profile was determined according to USP Item 711 "Dissolution" (see D1, apparatus 2 method A), at 37.5°C, 100 rpm, 120 minutes 0.1 H HCl and after 2 hours a phosphate buffer with 2% of sodium lauryl sulfate is added to bring up the pH to 6.8.

3.3 D2 are experiments filed by the appellant during the opposition proceedings. D2 shows in experiment 1 the dissolution profile of a tablet comprising rifaximin in the beta form, wherein only the acid dissolution stage was performed in the presence of sodium lauryl sulfate; this experiment highlights the absence of a delayed release under these specific experimental conditions. The conditions of the dissolution test were a stirring speed of 100 rpm; a temperature of 37 ± 0.5 °C, in a

dissolution media of 750 ml 0.1 N hydrochloric acid with 0.5% of sodium lauryl sulfate, and a duration of the test of 120 minutes. The dissolution medium is different from the experiment of Figure 4 of the patent, since sodium lauryl sulfate is present in the acidic medium of the test disclosed in D2, while in the patent it is added only later with the phosphate buffer.

The same test is made in experiment 2 of D2 according to USP, item 711 Dissolution (Apparatus 2, Method A Procedure), without the addition of sodium lauryl sulfate at pH 6.8. Experiment 2 shows a delayed release of rifaximin β after 120 minutes in moderate quantities.

A third experiment was performed in D2 comparing the dissolution profiles of tablets comprising rifaximin either in the polymorph state α or β; both dissolution profiles show a delayed release profile. The dissolution was determined according to USP, item 711 Dissolution (Apparatus 2, Method A Procedure), stirring speed, l00r pm; temperature 37 ± 0.5 °C; dissolution media, 0.1 N hydrochloric acid and after 120 min a phosphate buffer with 2% of sodium lauryl sulfate was added to bring up the pH to 6.8.

3.4 D3 is the Guidelines of EMA for the modified release products. In point 3.1. (page 10/16) D3 explains that "Several delayed release dosage forms have been identified by the Ph.Eur.: gastro-resistant capsules, tablets and granules. In this section, specific guidance is provided for gastro-resistant dosage forms. Products based on other principles can also often be classified as delayed release dosage forms, including those designed to release in a specific area of the

gastrointestinal tract in response to a specific trigger (e.g. enzymes) or at a specific time after ingestion". D23 confirms this definition and also mentions also that delayed release dosage forms comprise gastroenteric forms but are not limited thereto.

3.5 In the Board's view, the expression a "tablet for delayed release" broadly defines a tablet which delivers a drug with a delay after its administration; although the most frequent type of dosage forms reaching a delayed release are enteric or gastroresistant dosage forms, also other alternative form exist. This is confirmed explicitly by the disclosure of the cited passage of D3 (see point 3.4 above).

In the present case, the contested patent teaches that it is possible to provide a delayed release dosage form through the use of the specific polymorphic β form of rifaximin (see par. [0006]-[0008] of the specification). The delayed release of the claimed dosage form is shown in Figure 4 of the patent, through the use of the standard USP ITEM 711 dissolution test (see par. [0018]).

The Board does not see any valid reason to contest this standard USP dissolution test and the results obtained therewith, since this kind of test is the usual way to show a delayed release; the Board does also not see any reason to contest the use of sodium lauryl sulfate in the alkaline medium. The same dissolution test combining a release in an acidic medium followed by a medium at pH 6.8 and the presence of sodium lauryl sulfate (SLS) is for instance also used in example 6 of D6. D12 discloses furthermore the use of a dissolution

test in 6.8 phosphate buffer with 1.5% SLS, which proves that the use of SLS is standard in dissolution tests (see D12 par. [0014]). Hence, the arguments of the appellant regarding the dissolution test and the presence of SLS in the second dissolution medium appears irrelevant.

The Board was also not convinced by the experimental results shown in experiment 1 of D2, since said experiment was not done under standard test conditions in view of the presence of sodium lauryl sulfate in the acidic medium. On the other hand, experiments 2 and 3 confirms unambiguously the existence of a delayed release when a first acidic dissolution medium is used for the test.

Consequently, the Board does not see any reason to question the delayed release property of the claimed composition. The claimed invention is sufficiently disclosed and the main request meets the requirements of Article 83 EPC.

4. Main request - Inventive step

4.1 The claimed invention relates to an oral dosage form comprising rifaximin in form β, wherein the oral dosage form provides delayed release.

4.2 The opposition division considered D12 to be the closest prior art. The appellant also regards this document as a suitable closest prior art document for the assessment of inventive step.

In contrast, the respondent regards D6 as a more suitable starting point.

4.2.1 D12 discloses compositions of rifaximin or any salt, enantiomer or polymorph thereof, suitable for a once-a-day administration for treating a disease such as Crohn's disease (see D12, par. [0008],[0016], [0019]). D12 mentions that a coating may be present in order to release the drug at the required site of action, in particular to prevent a release in the mouth or oesophagus; D12 envisages coatings based on HPMC or gelatin which are used in most examples (see par. [0052]).

In a specific embodiment, D12 discloses a core with rifaximin and external layers (see par. [0060]-[0063]).

Moreover, D12 provides in examples 1, 3, 5 and 6 formulations free of enteric material; the in vitro dissolution study at pH 6.8 of example 3 is such that 20-50% of drug is released in about 8 hours, 30-70% in about 12 hours, and more than 70% in 24 hours (see par. [0139]).

D12 discloses that the therapeutic dose varies according to the body weight and the acuteness of the pathology. A daily dose can be between 20 and 2400 mg, preferably between 200 to 2000 mg, administered in a single dose or divided into 2 or 3 doses(cf. par. [0079] and [0080]). A once-daily dose of 600 mg is particularly mentioned. The examples of D12 do not specify the amount of drug used in the disclosed formulations, but only the percentage w/w% related to the total weight of the tablets. In examples 3 and 5, the relative amount of rifaximin is 50 w/w%, while in example 6, it is 60 w/w%.

This document does not disclose that rifaximin is in the polymorphic form β, and does not disclose a dosage of 700-900 mg on the basis of anhydrous rifaximin.

4.2.2 D6 discloses gastroresistant formulations of rifaximin which release rifaximin in the intestinal tract (see D6, page 6, 2nd par.). Rifaximin is selected from one of its polymorphic form, among which the β form (see page 14, 1st par.). The tablets disclosed in D6 comprise between 50 and 600 mg of rifaximin (see page 16, third par.).

Example 4 discloses the preparation of tablets made from gastroresistant microgranules with 400 mg of rifaximin. D6 does not disclose a tablet with 700-900 mg of the β polymorphic form of rifaximin and discloses only dosage forms with enteric material.

4.2.3 In view of the above analysis, the Board considers that the opposition division's choice of D12 as the closest prior art was appropriate.

4.3 The problem was defined by the opposition division as the provision of a high strength tablet formulation of rifaximin suitable for the treatment of Crohn's disease by once daily administration.

The appellant has defined the problem as the provision of an alternative tablet comprising rifaximin that does not contain enteric material.

According to the respondent, the problem is the provision of a high strength delayed release tablet suitable for the treatment of Crohn's disease by once daily administration and with enhanced patient compliance.

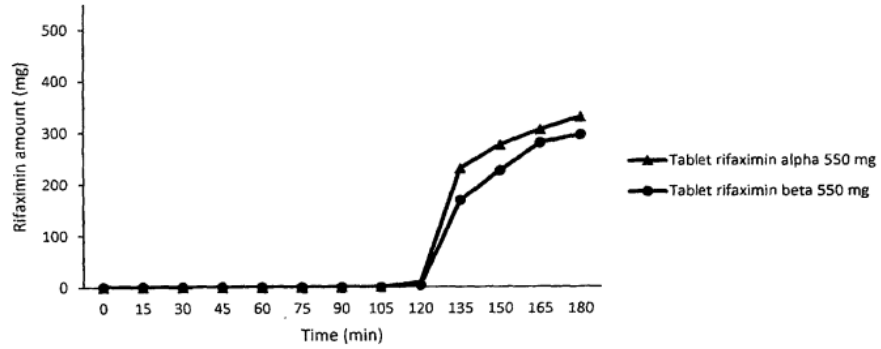
4.4 The solution to any of these problems is the use of the beta polymorphic form of rifaximin and a tablet dosage of 700-900 mg of rifaximin.

4.5 With regard to the technical effects linked with the distinguishing features, the opposition division concluded in its decision that no technical effect could be acknowledged for the choice of the polymorphic form β of rifaximin, and that the content of 700-900 mg of rifaximin β renders the tablet suitable for the treatment of Crohn's disease for once daily administration.

4.5.1 With regard to the specific β polymorphic of rifaximin, the contested patent mentions in paragraphs [0004] and [0005] that "the active pharmaceutical agent should be provided in a form having a low solubility and bioavailability for the best efficiency" and "the form of α rifaximin is reported to show an increased initial solubility". Moreover, paragraph [0006] and [0007] mention the low solubility of the β polymorphic form of rifaximin.

No effect linked with the choice of a specific polymorph form of rifaximin has however been demonstrated in the contested patent. On the contrary, D2 proves in its experiment 3 that tablets comprising the alpha polymorphic form of rifaximin provide the same delayed release than the β form, as shown below in Figure 3 of experiment 3:

Figure 3



Accordingly, the Board concurs with the conclusion of the opposition division that no particular effect can be acknowledged for the choice of the polymorphic form β of rifaximin.

4.5.2 With regard to the claimed content of 700-900 mg, it is credible that a high dosage tablet allows the administration of a higher dose in a single administration, even if compliance might also be dependent on further characteristics not present in the claims, such as the tablet size. Accordingly, the Board concurs with the definition of the problem as given by the opposition division in its decision(see point 4.3 above).

4.6 It remains to determine whether the claimed solution is obvious.

4.6.1 The polymorphic β form of rifaximin is known from D5 which suggests the preparation of solid dosage forms comprising this polymorphic form (see par. [0013], [0041]-[0043]), while the closest prior art D12 envisages to incorporate any polymorphic form in the tablets disclosed therein.

Accordingly, since there is no technical effect linked with the specifically claimed polymorphic form of rifaximin, the choice of the β form is an arbitrary choice which is obvious for the skilled person.

4.6.2 The claimed content of 700-900 mg of rifaximin in the tablet is also an obvious feature. In fact, there doesn't seem to be any technical prejudice against tablets with a higher drug content. There is nothing which would prevent the skilled person to prepare tablets with a large amount of rifaximin, even less when considering the technical teaching of D12.

D12 envisages to administer a daily dose between 20mg and 2400 mg, preferably 200mg to 2000mg, administered in a single dose or divided into 2 or 3 doses, depending on the body weight and the acuteness of the pathology (see par. [0079]). The relative amount of rifaximin is 60 w/w% in example 6, which corresponds to the minimum relative amount present in dependent claims 4 and 5 of the main request, i.e 60-95 wt%. A tablet containing e.g. 800 mg of rifaximin in a relative amount of 60% would have a total weight of around 1340 mg which falls within the ranges disclosed in paragraph [0061] of the patent. The claimed content of 700-900 mg is therefore obvious in view of D12 alone.

An oral dosage form having a strength comprised between 700 and 900 mg appears furthermore to be common for rifaximin. For instance, example 7 of D6 discloses a twice-a-day administration of 800 mg, i.e 1600 mg per day.. D22 (see "Study drugs" on page 1118) refers to rifaximin gastroresistant granules for oral administration containing 800 mg of active ingredient.

Consequently, the claimed tablet content of 700-900 mg of rifaximin is also obvious over the cited prior art.

4.7 The claimed subject-matter is therefore obvious in view of the cited prior art, and the main request does not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated