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Datasheet for the decision of 29 September 2021

Case Number: T 0634/19 - 3.3.01

Application Number: 13275196.7

Publication Number: 2702994

IPC: A61K31/4412, A61K31/496

Language of the proceedings: EN

Title of invention:
Methods of administering pirfenidone therapy

Patent Proprietor:
InterMune, Inc.

Opponents:
Alfred E. Tiefenbacher (GmbH & Co. KG)
Sandoz AG

Headword:
Pirfenidone-ciprofloxacin/INTERMUNE

Relevant legal provisions:
EPC Art. 54(5), 56

Keyword:
Second medical use (yes)
Inventive step - (no)

Decisions cited:
G 0002/08, T 0285/14

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Case Number: T 0634/19 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 29 September 2021

Appellant: (Patent Proprietor)	InterMune, Inc. 3280 Bayshore Boulevard Brisbane, CA 94005-1021 (US)
Representative:	Potter Clarkson The Belgrave Centre Talbot Street Nottingham NG1 5GG (GB)
Respondent: (Opponent 2)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 20 December 2018 revoking European patent No. 2702994 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	R. Romandini

Summary of Facts and Submissions

I. This appeal by the patent proprietor (appellant) is directed against the opposition division's decision revoking European patent No. 2 702 994 (patent in suit). The decision was based on the patent as granted and the claims of 11 auxiliary requests.

II. The following documents are referred to in the present decision.

D2 N. J. Carter, Drugs, 71(13), 2011, 1721-32

D4 Prescription information CIPRO®, Bayer Health Care Pharmaceuticals, 2011

D6 Assessment report for Esbriet® by EMA, 2010

D7 Guidance for Industry: Drug Interaction Studies, FDA, 2012

D12 Excerpt from British National Formulary, 61, 2011, 368-70

III. The patent had been granted with eight claims. Claim 1 as granted reads as follows:

"*1. Pirfenidone for use in treating a patient in need of pirfenidone therapy wherein the pirfenidone therapy comprises reducing the dosage of pirfenidone administered to a patient to 1602 mg/day during concomitant administration of ciprofloxacin at a dose of 750 mg twice daily (1500 mg/day).*"

IV. Two oppositions were filed against the patent on the grounds of Article 100(c), (b) and (a) EPC, for lack of novelty and inventive step.

In the decision under appeal, the opposition division concluded the following:

- Claim 1 of each of the main request and auxiliary requests 1 and 4 to 9 added subject-matter.
- Claim 1 of each of auxiliary requests 2 and 10 defined a first medical use and therefore its subject-matter lacked novelty.
- The subject-matter of claim 1 of auxiliary request 3 was not inventive starting from *inter alia* document D2.
- The additional auxiliary request filed during the oral proceedings was not admitted.

V. The appellant filed notice of appeal against this decision. With the statement of grounds of appeal, the appellant requested that the decision be set aside and that the oppositions be rejected, implying that the patent be maintained as granted (main request). Alternatively, the appellant requested that the patent be maintained in amended from on the basis of any of the following sets of claims:

- auxiliary request 1, filed on 4 December 2017
- auxiliary request 2, filed on 5 September 2018
- auxiliary request 3, filed at the oral proceedings on 9 November 2018
- auxiliary requests 4 to 9, filed as auxiliary requests 3 to 8 on 5 September 2018
- auxiliary request 10, filed at the oral proceedings on 9 November 2018
- auxiliary request 11, filed as auxiliary request 9 on 5 September 2018
- auxiliary requests 12 and 13, filed with the statement of grounds of appeal

Claim 1 of auxiliary request 1 differs from claim 1 as granted in that it specifies that the pirfenidone dosage is reduced from 2 400 or 2 403 mg/day.

Claim 1 of auxiliary request 2 differs from claim 1 as granted in that it specifies that the pirfenidone dosage is reduced from 2 403 mg/day.

Claim 1 of auxiliary request 3 differs from claim 1 of auxiliary request 2 in that it further specifies that the patient has idiopathic pulmonary fibrosis (IPF).

Claim 1 of auxiliary request 4 differs from claim 1 as granted in that it specifies that the patient is also in need of ciprofloxacin therapy for the treatment of a bacterial infection.

Claim 1 of auxiliary request 5 differs from claim 1 as granted in that it specifies that the pirfenidone therapy is for avoiding the potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

Claim 1 of auxiliary request 6 differs from claim 1 as granted in that it specifies that the patient has a fibrotic disorder, inflammatory disorder or autoimmune disorder.

Claim 1 of auxiliary request 7 differs from claim 1 as granted in that it specifies that the patient has IPF.

Claim 1 of auxiliary request 8 differs from claim 1 as granted in that it contains the amendments of auxiliary requests 4 and 6.

Claim 1 of auxiliary request 9 differs from claim 1 as granted in that it contains the amendments of auxiliary requests 4 and 7.

Claim 1 of auxiliary request 10 differs from claim 1 as granted in that it contains the amendments of auxiliary requests 3 and 5 and further specifies that the 2 403 mg/day pirfenidone are given as 801 mg three times per day and the 1 602 mg/day are given as 534 mg three times per day.

Claim 1 of auxiliary request 11 differs from claim 1 of auxiliary request 2 in that it specifies that the 2 403 mg/day pirfenidone are given as 801 mg three times per day and the 1 602 mg/day are given as 534 mg three times per day.

Claim 1 of auxiliary request 12 differs from claim 1 as granted in that it specifies that the patient is in need of pirfenidone therapy for the treatment of a fibrotic disorder, inflammatory disorder or autoimmune disorder.

Claim 1 of auxiliary request 13 differs from claim 1 as granted in that it specifies that the patient is in need of pirfenidone therapy for the treatment of IPF.

VI. In their replies to the statement of grounds of appeal, the opponents requested that the appeal be dismissed. Subsequently, with a letter dated 16 March 2021, opponent 1 withdrew its opposition and therefore ceased to be a party to these appeal proceedings.

Hence, opponent 2 is the sole respondent.

VII. The board scheduled oral proceedings in line with the parties' requests. In preparation for the oral proceedings, the board issued a communication drawing the parties' attention to salient issues that might be debated at the oral proceedings. In particular, it gave its preliminary opinion that the subject-matter of claim 1 as granted lacked inventive step starting from D2. This opinion applied to all requests on file.

VIII. Oral proceedings were held before the board on 29 September 2021. They took the form of a videoconference, as requested by the respondent. The appellant did not raise any objection in that respect.

IX. At the end of the oral proceedings, the board announced its decision.

X. The appellant's arguments, where relevant to the present decision, can be summarised as follows.

Claim 1 as granted defined a specific therapeutic use in accordance with Article 54(5) EPC (second medical use). G 2/08 (Reasons, 5.10.3) did not establish that a second medical use claim had to explicitly refer to a disease. This was confirmed by T 285/14. Therefore, the dosage regime in claim 1 had to be taken into account for the assessment of patentability.

Document D2 could be taken as the closest prior art. The subject-matter of claim 1 as granted differed from that prior art in that it specified the dosage regime of pirfenidone and ciprofloxacin. The inventors had found (patent, paragraphs [0008] and [0014] and Comparative Example 1) that ciprofloxacin at a dose of 750 mg twice daily increased pirfenidone exposure by a factor of about 1.8. The dosage regime proposed in

claim 1 avoided this higher exposure and reduced dose-dependent side effects or toxicity associated with pirfenidone (patent, paragraph [0028]). Therefore, the objective technical problem was to provide a safe pirfenidone therapy involving the concomitant administration of ciprofloxacin. The ciprofloxacin dose should not be included in the formulation of the problem – it was not disclosed in the closest prior art and was part of the solution.

The cited prior art did not render the solution proposed in claim 1 as granted obvious.

First, neither D6 nor D7 would have led the skilled person to conduct *in vivo* drug-drug interaction studies, let alone with ciprofloxacin. Section 2.7 of D6 disclosed a risk management plan out of which the skilled person would have needed to make several choices to arrive at the *in vivo* drug-drug interaction studies suggested at the top of page 78. The decision tree on page 16 of D7 would not have led the skilled person to conduct *in vivo* drug-drug interaction studies either because it also proposed other options, e.g. mechanistic modelling. Moreover, the choice of ciprofloxacin would have required additional selections. In particular, the skilled person would not have conducted *in vivo* studies with ciprofloxacin in view of the decision tree in D7 since ciprofloxacin was a strong CYP1A2 inhibitor (D7, page 41, Table 3) and *in vivo* drug-drug studies with a strong CYP1A2 inhibitor were already available, namely with fluvoxamine.

Second, if, for the sake of argument, the skilled person had conducted *in vivo* drug-drug interaction studies with ciprofloxacin, they would have found that the moderate increase in pirfenidone exposure caused by

ciprofloxacin co-administration did not justify a dose adjustment. According to D7 (paragraph bridging pages 39 and 40), a less than twofold increase in exposure which was not associated with serious safety concerns, did not require any dose adjustment.

Third, there was no pointer in the prior art towards reducing the pirfenidone dose to specifically 1 602 mg/day.

XI. The respondent's arguments, where relevant to the present decision, can be summarised as follows.

The dosage regime in claim 1 as granted was not limiting because the claim did not refer to a specific therapeutic use within the meaning of Article 54(5) EPC. In line with G 2/08 (Reasons, 5.10.3), claim 1 referred to a first medical use, not to a second medical use, and had to be construed as being directed to "*pirfenidone for use in treating a patient in need of pirfenidone therapy*". The rationale of T 285/14 was not applicable because, unlike in the case in hand, the use in the claim on which T 285/14 was based was specific – the claim referred to a patient group in need of both pirfenidone and fluvoxamine therapy.

Document D2 was the closest prior art. If claim 1 was considered to be a second medical use claim, its subject-matter differed from the use in D2 in that the pirfenidone dose was reduced to 1 602 mg/day when co-administered with ciprofloxacin at a dose of 750 mg twice daily. The *in vivo* drug-drug interaction study in the patent (Comparative Example 1) showed that co-administration of ciprofloxacin at 750 mg twice daily increased patients' exposure ($AUC_{0-\infty}$) to pirfenidone by

a factor of 1.8. Therefore, the effect of reducing the recommended pirfenidone dose from 2 403 to 1 602 mg/day was to lower the risk of patient overexposure to pirfenidone while maintaining an equivalent therapeutic effect (patent, paragraph [0028]). Accordingly, the objective technical problem to be solved was to provide a further safe regime for pirfenidone when administered together with 1 500 mg/day ciprofloxacin.

The solution proposed in claim 1 as granted was obvious. D2 taught (page 1721) that pirfenidone was indicated for treating IPF at a dose of 2 403 mg/day (801 mg three times daily). It also taught (page 1724, sentence bridging the two columns, and page 1725, Table II) that pirfenidone was predominantly (48%) metabolised by the enzyme CYP1A2 and that ciprofloxacin was a strong inhibitor of that enzyme. The skilled person was thus aware that co-administration of ciprofloxacin with pirfenidone could lead to adverse interactions, so special care had to be taken in the process (D2, page 1725, Table II and section "Potential Drug Interaction").

It was common general knowledge that the maximum and standard dose of ciprofloxacin for treating respiratory tract infections, i.e. the infections arising in pulmonary fibrosis, was 750 mg twice daily (D12, page 369, right-hand column, section "Dose"). Hence, the skilled person was prompted to investigate how a ciprofloxacin dose of 750 mg twice daily interacted with pirfenidone. This was also strongly recommended by the FDA in D7 (page 7, last paragraph) as a routine for drug development. Furthermore, D7 (page 16) showed a decision tree on the recommended drug-drug interaction studies in relation to CYP1A2, among other enzymes. Knowing that CYP1A2 was responsible for 48% of systemic

pirfenidone clearance and that ciprofloxacin was a strong CYP1A2 inhibitor (D7, page 41, Table 3), the decision tree recommended conducting routine *in vivo* drug-drug interaction studies, i.e. the studies shown in the patent. Contrary to the appellant's view, mechanistic modelling was not an alternative since this could not provide accurate results. Section V of D7 detailed how to carry out the *in vivo* studies. In doing so, the skilled person would have found that the standard ciprofloxacin dose increases pirfenidone exposure by 1.8 times. This meant that a patient receiving the recommended pirfenidone dose of 2 403 mg/day was exposed to levels equivalent to 4 325 mg/day (1.8 x 2 403 mg/day). In order to keep the original pirfenidone exposure level and reduce potential adverse effects, the skilled person would have reduced the recommended dose by a factor of 1.8, namely to 1 335 mg/day. However, as the commercial form of pirfenidone on the priority date was as 267 mg capsules (Esbriet®), then for the sake of patient compliance the skilled person would have reduced the dose from 2 403 mg/day (three capsules three times per day) to 1 602 mg/day (two capsules three times per day). In summary, the claimed pirfenidone dose was an obvious compromise between patient compliance and an acceptable level of pirfenidone exposure.

XII. The parties' final requests were as follows.

The appellant requested that the decision be set aside and that the opposition be rejected, implying that the patent be maintained as granted (main request).

Alternatively, the appellant requested that the patent be maintained in amended form on the basis of one of the following claim requests:

- auxiliary request 1, filed on 4 December 2017
- auxiliary request 2, filed on 5 September 2018
- auxiliary request 3, filed at the oral proceedings on 9 November 2018
- auxiliary requests 4 to 9, filed as auxiliary requests 3 to 8 on 5 September 2018
- auxiliary request 10, filed at the oral proceedings on 9 November 2018
- auxiliary request 11, filed as auxiliary request 9 on 5 September 2018
- auxiliary requests 12 and 13, filed with the statement of grounds of appeal

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible. It meets the requirements of Articles 106 to 108 and Rule 99(2) EPC.

2. Interpretation of claim 1 as granted - Article 54(4) vs 54(5) EPC

2.1 Under Article 54(4) EPC, a substance or composition, comprised in the state of the art, for use in a method referred to in Article 53(c) EPC can be deemed to be novel, provided that its use for any such method is not comprised in the state of the art (first medical use).

Article 54(5) EPC establishes that a substance or composition referred to in Article 54(4) EPC for any specific use in a method referred to in

Article 53(c) EPC can be deemed to be novel, provided that such use is not comprised in the state of the art (second medical use).

2.2 According to the respondent (reply to the statement of grounds of appeal, paragraph 20), claim 1 as granted did not define a second medical use within the meaning of Article 54(5) EPC. The claim did not specify the treatment of a disease but rather was generally directed to "*pirfenidone for use in treating patients in need of pirfenidone therapy*". Therefore, claim 1 defined a first medical use in accordance with Article 54(4) EPC. This view was in line with G 2/08 (Reasons, 5.10.3). The rationale of decision T 285/14 (Reasons, 1.3.4) could not apply to the case in hand because the claim on which T 285/14 was based defined a restricted patient group characterised by its need for both pirfenidone and fluvoxamine therapy.

2.3 It is true that claim 1 does not explicitly refer to any disease. Nevertheless, it does not follow from the wording of Article 54(5) EPC that the new specific use needs to refer to a disease. This cannot be derived from G 2/08 either. In G 2/08 (Reasons, 5.10.3), the Enlarged Board simply concluded that the new specific use was in principle not confined to a particular indication and that, therefore, the new use did not need to be the treatment of another disease. This does not imply that a specific use must refer to a disease.

2.4 The board agrees with the appellant that claim 1 defines a specific therapeutic use within the meaning of Article 54(5) EPC despite not mentioning any disease.

Contrary to the respondent's view, claim 1 is not merely directed to the use of pirfenidone for treating patients in need of pirfenidone therapy. It is clear from the claim wording that the target patients are in need of both pirfenidone and ciprofloxacin therapy. On the priority date, pirfenidone and ciprofloxacin were two medicaments approved for different therapeutic indications: pirfenidone was an anti-fibrotic (patent, paragraph [0002]) and ciprofloxacin was a well-known antibiotic (D12, page 368, right-hand column, paragraph 2). Therefore, the patients according to claim 1 suffer from both a fibrotic condition and a bacterial infection. Furthermore, claim 1 implicitly requires that, before being treated with the combination of pirfenidone and ciprofloxacin, the patients had been treated with pirfenidone only, at a dose higher than 1 602 mg/day. These patients constitute a restricted subgroup within the patients in need of pirfenidone, thus rendering the claimed therapeutic use specific.

This reasoning is in line with decision T 285/14 (Reasons, 1.3.4). In that decision, the board concluded that a claim directed to treating patients in need of both pirfenidone and fluvoxamine therapy defined a specific therapeutic use despite the claim not explicitly mentioning any disease.

2.5 Consequently, the board holds that claim 1 as granted relates to a specific medical use in conformity with Article 54(5) EPC and that its dosage regime must be considered for the assessment of patentability.

3. Inventive step - claim 1 as granted

3.1 Claim 1 as granted is directed to a specific dosage regime for the concomitant use of pirfenidone and

ciprofloxacin. Pirfenidone is an orally active anti-fibrotic compound sold in several European countries under the trade name Esbriet® and approved for treating IPF (patent, paragraph [0002]). It is primarily metabolised by the enzyme CYP1A2 (patent, paragraph [0031]). Ciprofloxacin is a broad-spectrum antimicrobial agent which inhibits CYP1A2 (patent, paragraphs [0004] and [0005]).

The claimed invention (patent, paragraphs [0008], [0014], [0026], [0028] and [0033]) is based on the appellant's finding that the co-administration of pirfenidone with 750 mg ciprofloxacin twice daily increases patients' exposure to pirfenidone by a factor of about 1.8. This is a consequence of the inhibition of CYP1A2 by ciprofloxacin, which reduces pirfenidone clearance. As a consequence, a patient receiving the recommended pirfenidone dose of 2 403 mg/day would be exposed to pirfenidone levels equivalent to a dose of about 4 325 mg/day (1.8 x 2 403 mg/day) when ciprofloxacin is co-administered. To avoid such an increase in pirfenidone exposure and the associated potential adverse effects, claim 1 proposes that the pirfenidone dose be reduced to 1 602 mg/day when used in combination with ciprofloxacin at a dose of 750 mg twice daily.

3.2 The board agrees with the parties that D2 is a suitable starting point for assessing inventive step.

D2 is a monograph on pirfenidone and its use in IPF. It teaches (page 1721, and page 1724, passage bridging the two columns) that pirfenidone is administered orally at a dose of 2 403 mg/day, as 801 mg three times a day, and that 48% of pirfenidone is metabolised by the enzyme CYP1A2. Therefore, special care should be taken

if combining pirfenidone with strong to moderate CYP1A2 inhibitors, e.g. ciprofloxacin, due to a potential drug interaction (page 1725, section "Potential Drug Interactions" and Table II).

3.3 It was undisputed that the subject-matter of claim 1 differs from the content of D2 on account of the specific dosage regime proposed for the co-administration of pirfenidone and ciprofloxacin. The parties also agreed that the effect associated with this difference was to reduce the potential adverse effects caused by increased exposure to pirfenidone while maintaining an equivalent therapeutic effect.

3.4 On the basis of this difference, the appellant defined the objective technical problem as providing a safe dosage regime for the concomitant administration of pirfenidone and ciprofloxacin.

The respondent defined the problem in a similar way but included the dosage of 750 mg ciprofloxacin twice a day in its wording.

On this point, the board concurs with the appellant that the dosage of ciprofloxacin is not disclosed in the closest prior art. It makes part of the solution, the inventive character of which must be assessed, and not of the problem solved by that solution. Accordingly, the board agrees with the objective technical problem as formulated by the appellant.

3.5 Nevertheless, the board considers that the solution proposed in claim 1 was obvious to the skilled person.

3.5.1 On the priority date, it was common general knowledge that the maximum recommended dose of ciprofloxacin was

750 mg twice a day. This was also the standard dose for severe or complicated respiratory tract infections (D4, table on page 24, and D12, page 369, section "Dose"), which are the kind of infections generally associated with IPF. This was not disputed by the appellant (statement of grounds of appeal, section 6.5, paragraph 3).

Therefore, starting from D2, which deals with the treatment of IPF, it is reasonable to assume that the skilled person faced with the objective technical problem was particularly interested in a pirfenidone dosage regime where ciprofloxacin was administered at a dose of 750 mg twice daily.

3.5.2 It was known from D2 that CYP1A2 is responsible for metabolising 48% of the systemic pirfenidone and that ciprofloxacin is a moderate or strong CYP1A2 inhibitor. For this reason, the author of D2 warned about the risk of interaction between pirfenidone and ciprofloxacin. This concern was also shared by the EMA in D6, its assessment report on Esbriet® (hard capsules containing 267 mg pirfenidone; see D6, page 9, paragraph 3). The report stated (page 24, section "Metabolism"; page 25, penultimate paragraph; page 23, Table 5.2-1, Study No. PIPF-010) that significant decreases in pirfenidone clearance had been observed in healthy subjects upon co-administration of CYP1A2 inhibitors. In particular, the strong CYP1A2 inhibitor fluvoxamine had shown a sixfold increase in exposure to pirfenidone ($AUC_{0-\infty}$).

3.5.3 Hence, the skilled person searching for a safe dosage regime for the co-administration of pirfenidone and ciprofloxacin was compelled from the outset to determine what effect ciprofloxacin actually had on pirfenidone clearance, especially when ciprofloxacin

was administered at the recommended dose of 750 mg twice daily.

3.5.4 Under these circumstances, the board agrees with the respondent (reply to the statement of grounds, paragraph 38 and section 5.4.1) that the obvious measure to take was to conduct *in vivo* drug-drug interaction studies. Indeed this is the most suitable way of properly and accurately assessing the potential interactions between two well-known, commercial drugs. In this context, the appellant's argument that mechanistic modelling would be an alternative is not realistic. It is notorious that modelling cannot replace real tests to obtain actual interactions between drugs. Furthermore, D6 and D7 show that *in vivo* studies are customary in the context of drug development and pharmacovigilance. They do not entail any undue burden for the skilled person.

D6 discloses (page 25, penultimate paragraph) the results of *in vivo* drug-drug interaction studies between pirfenidone and fluvoxamine and proposes (top of page 78) conducting the same studies with moderate CYP1A2 inhibitors to assess the impact on pirfenidone pharmacokinetics and safety in healthy subjects. D7 indicates (page 7, last paragraph) that, following *in vitro* tests, *in vivo* interaction studies have become an integral part of drug development and regulatory review. The decision tree on page 16 of D7 proposes *in vivo* drug-drug interaction studies when *in vitro* studies show that an enzyme, e.g. CYP1A2, is responsible for at least 25% of drug clearance. In the case in hand, *in vitro* studies had already shown that CYP1A2 cleared 48% of pirfenidone.

3.5.5 By carrying out *in vivo* drug-drug interaction studies, the skilled person would have arrived at the result presented in Comparative Example 1 of the patent, namely that co-administration of ciprofloxacin at a dose of 750 mg twice daily increased pirfenidone exposure 1.8 times.

This result would have rendered it apparent that, to maintain the therapeutic effect of pirfenidone at the level of the standard dose of 2 403 mg/day without increasing the risk of adverse effects, the pirfenidone dose had to be reduced by a factor of 1.8 to 1 335 mg/day.

3.5.6 As noted by the respondent (reply to the statement of grounds of appeal, section 5.4.5), on the priority date pirfenidone was marketed as hard capsules containing 267 mg of active ingredient each, and was administered at 2 403 mg/day as three capsules (801 mg) three times a day (D2, page 1721 and page 1730, footnote "a" of Table VI; D6, page 6, paragraph 4 and page 23, Table 5.2-1). Considering the importance of patient compliance for the success of a therapeutic treatment and the fact that 1 335 is not a multiple of 267, the skilled person would have reduced the dose to an amount close to 1 335 mg/day administrable by a whole number of capsules. In this context, the choice of 1 602 mg/day, i.e. two capsules three times a day, was a good compromise between an acceptable level of pirfenidone exposure and patient compliance. Hence, it was obvious to reduce the pirfenidone dose from 2 403 mg/day (three capsules three times a day) to 1 602 mg/day (two capsules three times a day) when ciprofloxacin was to be co-administered at a dose of 750 mg twice daily.

3.6 The appellant argued that the cited documents would not have led the skilled person to conduct *in vivo* drug-drug interaction studies, let alone with ciprofloxacin. Moreover, even if they had carried out *in vivo* studies, they would not have concluded that the pirfenidone dose needed to be adjusted, even less to the extent proposed in claim 1.

3.6.1 In the appellant's view, neither D6 nor D7 would have prompted the skilled person to carry out *in vivo* drug-drug interaction studies.

- In section 2.7 of D6, the skilled person was presented with a comprehensive risk management plan. To arrive at the drug-drug interaction studies suggested at the top of page 78, multiple selections were needed: first, studying "important potential risks"; second, focusing on "potential drug interactions (including smoking)"; third, opting to conduct drug-drug interaction studies among other choices.

- As to D7, following the decision tree on page 16 the skilled person would not have necessarily carried out *in vivo* drug-drug interaction studies since studies of this kind with a strong CYP1A2 inhibitor (fluvoxamine) were already available, and the tree proposed other options for less strong inhibitors, e.g. mechanistic modelling.

The board disagrees. As outlined above (point 3.5), the motivation for the skilled person to conduct *in vivo* drug-drug interaction studies was the knowledge in the prior art that pirfenidone is predominantly cleared by CYP1A2 and that ciprofloxacin inhibits CYP1A2. On the basis of this knowledge, the skilled person would infer

that an interaction between ciprofloxacin and pirfenidone was highly likely. Furthermore, it is apparent that any such interaction can only be properly assessed by *in vivo* studies. The fact that D6 and D7 mention these studies is relevant merely in that the documents show that conducting *in vivo* drug-drug interaction studies is a customary measure carried out routinely when, as in the case in hand, there is clear evidence of the risk of drug interaction.

3.6.2 The appellant's argument that the choice of ciprofloxacin for conducting *in vivo* drug-drug interaction studies would have required multiple selections is beside the point. The skilled person was seeking to solve the objective technical problem, which is specifically concerned with the co-administration of ciprofloxacin.

3.6.3 The appellant also argued that, even if *in vivo* interaction studies had been carried out, the skilled person would not have concluded that the pirfenidone dose needed to be adjusted. This was because D7 (paragraph bridging pages 39 and 40) taught that a dose adjustment was only required if the increase in patient exposure was at least twofold, or if it could be associated with serious safety concerns. In the case in hand, neither of these conditions was met.

The board notes that this argument is based on an incorrect premise, namely that the skilled person was investigating whether the pirfenidone dose on the product label needed adjusting. This was indeed the context of D7, which provides guidance for industry regarding drug interaction studies and their implications for dosing and labelling. However, the appellant's argument overlooks the fact that the

skilled person's motivation was not marketing or labelling matters but the will to solve the objective technical problem. Hence, the appellant's argument cannot counter the conclusion that the result of the *in vivo* drug-drug interaction studies would have led the skilled person faced with the objective technical problem to reduce the pirfenidone dose.

3.6.4 The issue of the magnitude of the dose reduction has already been dealt with in point 3.5.6.

3.7 Consequently, the board holds that the subject-matter of claim 1 as granted lacks inventive step and does not meet the requirements of Article 56 EPC.

4. Admittance of auxiliary requests 10, 12 and 13

Auxiliary request 10 was first filed at the oral proceedings before the opposition division and was not admitted. It was re-filed with the statement of grounds of appeal.

Auxiliary requests 12 and 13 were filed for the first time with the statement of grounds of appeal.

In view of the outcome of the assessment of inventive step in relation to these requests (see point 5), the board does not need to give details on the reasons for its decision to admit the requests into the appeal proceedings pursuant to Article 12(4) RPBA 2007.

5. Inventive step - Auxiliary requests

The appellant did not provide any additional inventive-step arguments in relation to the subject-matter

claimed in the auxiliary requests, either in writing or at the oral proceedings before the board.

5.1 The following limitations in the claims of the auxiliary requests do not constitute any additional difference from the closest prior art (D2) and hence cannot contribute to inventive step:

- The pirfenidone dose before ciprofloxacin administration was 2 403 mg/day given as 801 mg three times per day.
- The patient has IPF or is in need of pirfenidone therapy to treat IPF.
- The patient has a fibrotic disorder or is in need of pirfenidone therapy to treat a fibrotic disorder.

Accordingly, the subject-matter of claim 1 of each of auxiliary requests 1 to 3, 6, 7, 12 and 13 lacks inventive step for the reasons put forward in relation to claim 1 as granted.

5.2 Claim 1 of each of auxiliary requests 4, 8 and 9 further specifies that the patient is also in need of ciprofloxacin therapy to treat a bacterial infection.

On the priority date, ciprofloxacin was a well-known broad-spectrum antibiotic (see point 3.1) and, as such, its primary use was in treating bacterial infections. Therefore, the specification in auxiliary requests 4, 8 and 9 that the therapeutic purpose of ciprofloxacin is to treat bacterial infection cannot contribute to inventive step.

5.3 Claim 1 of auxiliary requests 5 and 10 specifies that pirfenidone therapy is intended for avoiding the

potential for a reduced clearance of pirfenidone or the potential for an increased exposure to pirfenidone.

As outlined in point 3.5.2 above, the skilled person was aware that the co-administration of pirfenidone and ciprofloxacin could make it necessary to reduce the pirfenidone dose in order to avoid the potential for an increased exposure resulting from a reduced clearance of pirfenidone due to the inhibition of CYP1A2 by ciprofloxacin. Hence, specifying this purpose in the claims cannot render the claimed subject-matter inventive either.

5.4 Claim 1 of auxiliary request 11 contains the additional feature that the pirfenidone dose of 1 602 mg/day is given as 534 mg three times per day.

The dose 534 mg means two 267 mg capsules. Therefore, auxiliary request 11 merely claims that the pirfenidone dose is reduced to two capsules three times a day. This was obvious, as already explained in the context of claim 1 as granted (point 3.5.6).

5.5 As a consequence, none of the auxiliary requests meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated