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Datasheet for the decision of 8 December 2020

Case Number: T 1937/18 - 3.3.01

Application Number: 01949158.8

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Title of invention:
A NEW USE FOR DEFERIPRONE

Patent Proprietor:
Chiesi Farmaceutici S.p.A.

Opponents:
Lipomed AG
Lipomed GmbH

Headword:
Deferiprone/CHIESI

Relevant legal provisions:
EPC Art. 56, 105

Keyword:
Inventive step (no) - reasonable expectation of success

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Case Number: T 1937/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 8 December 2020

Appellant: (Patent Proprietor)	Chiesi Farmaceutici S.p.A. Via Palermo 26/A 43122 Parma (IT)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent 1: (Opponent)	Lipomed AG Fabrikmattenweg 4 4144 Arlesheim (CH)
Representative:	Ciesla, Ulrike Meyerlustenberger Lachenal AG Schiffbaustrasse 2 8031 Zürich (CH)
Respondent 2: (Intervener)	Lipomed GmbH Hegenheimer Strasse 2 79576 Weil am Rhein (DE)
Representative:	Ciesla, Ulrike Meyerlustenberger Lachenal AG Schiffbaustrasse 2 8031 Zürich (CH)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 16 July 2018 revoking European patent No. 1294379 pursuant to Article 101(3)(b) EPC**

Composition of the Board:

Chairman	A. Lindner
Members:	J. Molina de Alba
	M. Blasi

Summary of Facts and Submissions

I. This appeal lies from the opposition division's decision to revoke European patent No. 1 294 379.

II. The patent had been opposed on the grounds of insufficiency of disclosure, lack of patentability within the meaning of Articles 52(2) and 53(c) EPC, lack of novelty and lack of inventive step.

This is the second appeal concerning this patent. In the earlier decision T 195/12, the decision under appeal was limited to the issue of novelty and the appeal was allowed.

III. The documents cited by the parties during these appeal proceedings include the following:

D2: G.J. Kontoghiorghes et al., The Lancet, 1987, 329(8545), 1294-5

D3: N.F. Olivieri et al., Blood, 1994, 84(10), Suppl. 1, 109A

D4: O. Diav-Citrin et al., Pediatric Clinics of North America, 1997, 44(1), 235-47

D5: B. Wonke et al., British Journal of Haematology, 1998, 103, 361-4

D6: F. Tricta et al., N. Engl. J. Med., 1998, 339(23), 1710-4

D7: G. Link et al., J. Lab. Clin. Med., 1999, 133(2), 179-88

D8: Y. Aydinok et al., Acta Haematol., 1999, 102, 17-21

D9: M.B. Agarwal et al., 10th International Conference on Oral Chelators in the Treatment of

Thalassaemia and Other Diseases and Biomed Meeting, Limassol (Cyprus), 22-26 March 2000

D10: L. De Franceschi et al., J. Lab. Clin. Med., 1999, 133(1), 64-9

D11: P. Töndury et al., 6th International Conference on Thalassaemia and the Haemoglobinopathies, Malta, 5-10 April 1997

D12: G.J. Kontoghiorghes et al., 10th International Conference on Oral Chelators in the Treatment of Thalassaemia and Other Diseases and Biomed Meeting, Limassol (Cyprus), 22-26 March 2000

D14: A. Piga et al., Blood, 1998, 92(10) part 1, abstract No. 3065

D15: H. Perrimond et al., Ann. Pediatr., 1991, 38(3), 175-84, abstract

D15a: Full document of D15 and English translation

D17: N.F. Olivieri et al., Blood, 1998, 92(10) Suppl. 1, abstract No. 2184

D20: N.F. Olivieri et al., Annals of the New York Academy of Sciences, 1998, 850, 217-22

D21: N.F. Olivieri et al., N. Engl. J. Med., 1998, 339(7), 417-23

D22: C. Borgna-Pignatti et al., Blood, 2006, 107(9), 3733-7

D23: L.J. Anderson et al., Eur. Heart J., 2001, 22, 2171-9

D25: Declaration of R. Galanello dated 30 March 2012

D26: Declaration of D. Pennell dated 30 March 2012

D29: The Thalassaemia Syndromes, D.J. Weatherall et al., 4th Ed., Blackwell Science Ltd., 2001, 649-51

D31: N.F. Olivieri et al., N. Engl. J. Med., 1994, 331(9), 574-8

D42: N.F. Olivieri et al., Blood, 1995, 86 (10 Suppl. 1), 249a, abstract 983

D43: D. Matsui et al., 94th Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Hawaii, March 1993, PI-43

D44: P. Mazza et al., Haematologica, 1998, 83, 496-501

D46: M. de Montalembert, Transfus. Clin. Biol., 1998(5), 353-6

D46a: English translation of D46

D47: N.F. Olivieri et al., Blood, 1992, 79(10), 2741-8

D48: P.J. Ho et al., British Journal of Haematology, 1998, 100, 70-8

D49: R. Galanello et al., Blood, 2006, 108(11), abstract No. 3822

D50: Piga et al., Haematologica, 2003, 88(05), 489-96

A2: Notice of infringement proceedings against Lipomed GmbH

A3: Notification of delivery signed on 13 November 2019

A6: A.V. Hoffbrand et al., Blood, 1998, 91(1), 295-300

IV. The decision under appeal was based on the claims of a main request and six auxiliary requests. The opposition division considered that the subject-matter of the main request and of auxiliary requests 2 and 4-6 was not inventive starting from document D4 as the closest prior art. The subject-matter of auxiliary requests 1 and 3 was not novel.

V. The patent proprietor (appellant) filed an appeal against this decision.

With the statement of grounds of appeal, the appellant maintained all the claim requests on which the decision was based.

In a subsequent letter dated 12 September 2019, it filed document D49.

VI. In its reply to the statement of grounds of appeal, the opponent (respondent 1) requested that the appeal be dismissed. It also filed documents D47 and D48.

VII. On 11 February 2020, Lipomed GmbH (respondent 2) filed a notice of intervention, paid the opposition fee and requested that the appeal proceedings be accelerated.

In the notice of intervention, respondent 2 referred to all the documents previously on file and introduced additional evidence including documents A2, A3 and A6. It raised new objections of added subject-matter, lack of novelty, lack of inventive step and insufficiency of disclosure.

VIII. By a communication dated 13 March 2020, annexed to the summons to oral proceedings scheduled in view of the parties' requests to that effect, the board informed the parties that respondent 2's request for acceleration of the proceedings had been granted.

In a communication dated 8 May 2020 sent in preparation for the oral proceedings, the board gave its preliminary opinion on the case.

IX. With its reply to the notice of intervention dated 8 July 2020, the appellant filed document D50 and 21 sets of claims designated as MR-a, MR-b, MR-ab, AR1-a to AR6-a, AR1-b to AR6-b and AR1-ab to AR6-ab.

Claims 1 and 14 of request MR-a read as follows:

"*1. Use of a therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof for manufacture of a medicament containing said therapeutically effective amount sufficient to chelate iron accumulation in the heart and prevent further iron accumulation in the heart for cardio-selective treatment or reversal of cardiac disease in a transfusion dependent thalassemia patient having iron induced cardiac disease said therapeutic amount being sufficient to reduce the iron stores in the heart and in preference to less critical organs/tissues in the body.*"

"*14. A therapeutically effective amount of deferiprone or a physiologically acceptable salt thereof sufficient to chelate iron accumulation in the heart and prevent further iron accumulation in the heart for use in cardio-selective treatment or reversal of cardiac disease in a transfusion dependent thalassemia patient having iron induced cardiac disease said therapeutic amount being sufficient to reduce the iron stores in the heart and in preference to less critical organs/tissue in the body.*"

X. Oral proceedings were held before the board on 8 December 2020. During the oral proceedings, the appellant made request MR-a its main and sole request. All other claim requests were withdrawn.

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

D4 is the closest prior art. However, the skilled person would not have placed weight on the statement in D4 in relation to reference 59 (page 239, section "Improvement in Organ Function") that the patient's

cardiomyopathy was iron-related and that cardiac iron had been decreased, as measured by MR imaging. Reference 59 is document D47 in these proceedings. It concerns a patient having thalassemia intermedia, i.e. not being transfusion-dependent. It was published in 1992, and at that time MR imaging was not validated as a method for quantifying cardiac iron (see D15a, paragraph below Figure 4): validation was first published in 2001 (D23, abstract and page 2178, section "Conclusions"). Moreover, the experimental data in D47 (page 2743, section "Quantitative MR image-derived parameters", and page 2744) do not support the conclusions drawn in it and reported in D4.

The objective technical problem is the provision of means for the effective treatment or reversal of cardiac disease in a transfusion-dependent patient having iron-induced cardiac disease.

The use of deferiprone proposed in claim 1 solves the problem, as demonstrated by the evidence in the patent and in post-published documents D22 and D50.

The skilled person would not have expected deferiprone to be able to solve the problem for two reasons: firstly due to the essential differences between thalassemia major (claim 1) and thalassemia intermedia (D4), and secondly because on the priority date the general opinion in the scientific community was that deferiprone was unable to reduce iron levels sufficiently to protect thalassemia major patients from iron-induced cardiac disease.

Regarding the first reason, the alleged improvement in cardiac function of a thalassemia intermedia patient having an iron-induced cardiomyopathy in D4 could not

be extrapolated to a thalassemia major patient. The differences between thalassemia major and thalassemia intermedia were common general knowledge, and the treatment of thalassemia major was known to be more challenging, especially regarding cardiac function. Thalassemia major patients are transfusion-dependent, whereas thalassemia intermedia patients are not. Therefore the former receive considerably higher amounts of iron and are at higher risk of iron overload. Furthermore, thalassemia major patients receive iron directly by transfusion, which favours accumulation in the heart. In contrast, iron absorption in thalassemia intermedia patients occurs mainly through the gut, so iron accumulates in preference in the liver (D44, page 500, right-hand column; D49).

The second reason results from the chronological development of knowledge in the technical field.

Between 1993 and 1997, deferiprone was considered a promising chelator for reducing cardiac iron accumulation because it had been shown to reduce serum ferritin and hepatic iron concentration (for serum ferritin: D31, page 576, right-hand column, lines 6-10, and D43; for hepatic iron concentration: D3, lines 5-6, and D4, page 239, section "Changes in Hepatic Iron Concentration"). The latter parameters were regarded as the standard indicators for iron-induced cardiac disease in those years.

This positive perception of deferiprone changed rapidly in 1998 when, following the results observed in several clinical studies, a series of publications drew attention to the potential cardiac damage that long-term treatment with deferiprone could cause in thalassemia major patients (see D17, abstract 2184,

last two sentences; D20, page 219, lines 1-2 and paragraph 3, and page 220, lines 12-17 and 28-31; D21, paragraph bridging pages 420 and 421; D46a, page 6, paragraph 2, last sentence; A6, summary, right-hand column, lines 7-11, and page 299, left-hand column, lines 4-8). It then became clear that serum ferritin and hepatic iron concentration were poor indicators of cardiac iron loads. This was acknowledged and confirmed in the patent (paragraph [0096]). Subsequently, it was observed that serum ferritin and hepatic iron concentration do indeed not correlate with cardiac iron load (see D23, page 2178, section "Conclusions"; D26, paragraph 13).

Thus on the priority date the general opinion in the field was that deferiprone was not suitable for treating iron-induced cardiac diseases, and that it increased the risk of cardiac fibrosis.

This opinion did not change after the publication of D9 in 2000, which disclosed a long-term clinical study on deferiprone. D9 was merely an abstract and disclosed neither whether the patients had iron-induced cardiac disease at the outset of the treatment nor whether the treatment had a positive or negative impact on the heart.

Document D29, which is an excerpt from a textbook published shortly after the priority date, reflects the general knowledge on that date. It stated (page 651, left-hand column, paragraph 2) that there was good experimental evidence that compounds closely related to deferiprone could cause fibrosis. Also, Professor Galanello declared (D25, paragraph 5) that in 2001 he sought approval to undertake a clinical study involving deferiprone in combination with desferrioxamine, and

that cardiac disease was an exclusion criterion set by the ethics committee because there was no evidence that deferiprone was beneficial to the heart.

The skilled person would not have ignored the warnings in 1998 and subsequent publications, and would have refrained from using deferiprone to treat thalassemia major patients having iron-induced cardiac disease.

XII. The respondents' arguments, where relevant to the present decision, may be summarised as follows.

Document D4 is the closest prior art. It cites reference 59, which is D47 in these proceedings. The appellant's interpretation of D47 and of the weight that the skilled person would have placed on its conclusions is flawed. The skilled person had no reason to question the conclusions in D47, which was a peer-reviewed paper. Nor did the authors of D4 do so.

If sufficiency of disclosure were acknowledged, the objective technical problem would be, as formulated by the opposition division, the provision of means for the effective treatment or reversal of cardiac disease in a transfusion-dependent patient having iron-induced cardiac disease.

The skilled person would have had reasonable expectations that deferiprone would solve the problem posed.

Firstly, regardless of the patient's dependency on blood transfusions and the iron absorption route, on the priority date iron-induced cardiac disease caused by thalassemia major or thalassemia intermedia

exhibited the same symptoms and was treated in the same manner, namely by iron chelation.

Secondly, the treatment of thalassemia major with deferiprone was known before the priority date. This was acknowledged in the patent (paragraph [0006]) and disclosed in many of the prior-art documents cited in these proceedings (see abstracts of D2-D12, D14, D15/ D15a and D42-D44). Hence the skilled person would have expected deferiprone to successfully treat iron-induced cardiac disease associated with thalassemia major.

Contrary to the appellant's allegation, in 1998 there was no change of opinion in relation to the ability of deferiprone to chelate cardiac iron in thalassemia major patients. Before 1998, many documents disclosed successful treatment of thalassemia major with deferiprone. This was summarised in 1997 in the review paper D4. But even in 1998 and afterwards deferiprone was reported to be suitable for treating thalassemia major patients (see e.g. D14; D44, page 500, last paragraph; D9): even the patent's inventors published a letter in 1998 (D6) in which they questioned the warning in D21 against the side-effects of deferiprone when treating thalassemia major. D9 was particularly relevant because it disclosed shortly before the priority date the results of a long-term clinical study.

XIII. The parties' final requests were as follows.

- The appellant requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the set of claims of the main request, filed as MR-a with

the letter dated 8 July 2020.

- The respondents requested that the appeal be dismissed.

XIV. At the end of the oral proceedings, the board's decision was announced.

Reasons for the Decision

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

2. Intervention

On 11 February 2020, Lipomed GmbH filed a notice of intervention including documents A2 and A3 as evidence. The opposition fee was paid on the same date.

Document A2 is a letter dated 7 November 2019 by which the appellant instituted proceedings against Lipomed GmbH for infringement of European patent No. 1 294 379 in Germany. Document A3 is a notification delivered on 13 November 2019 in which the competent court (Landgericht Düsseldorf) informed Lipomed GmbH that infringement proceedings were being instituted.

The intervention met the requirements of Article 105(1)(a) EPC and Rule 89 EPC, and was therefore treated as an opposition (Article 105(2) EPC).

3. Admittance of the main request

The main request comprises the set of claims filed by the appellant as "MR-a" with the letter dated 8 July 2020. The respondents did not object to its admittance.

The main request was a legitimate attempt by the appellant to address an added-matter objection raised for the first time with the notice of intervention. The request was filed on the first possible occasion and its admission was beneficial to procedural economy.

Therefore the board admitted MR-a into the appeal proceedings pursuant to Article 13(1) RPBA.

4. Documents D47-D50

Documents D47-D49 were submitted by respondent 2 with its notice of intervention (page 10, section V).

Document D50 was filed by the appellant with its reply to the notice of intervention, hence at the earliest possible stage. The respondents did not object to its admission and the board had no reasons not to take D50 into account.

5. Inventive step

5.1 The patent concerns the treatment of patients who need regular transfusions of red blood cells such as thalassemia major patients. These patients are exposed to an excess of iron, which is dangerous because iron cannot be excreted sufficiently and accumulates, causing toxic degenerative changes in the heart, liver

and endocrine organs. Thus thalassemia major patients have to be treated with an iron chelator which enhances iron excretion.

In particular, the patent concerns the use of deferiprone as an iron chelator for reducing cardiac iron stores in transfusion-dependent thalassemia patients who have iron-induced cardiac disease.

5.2 It was common ground among the parties that document D4 was a suitable starting point for assessing inventive step.

D4 is a review paper published in 1997 on the use of deferiprone as an iron chelator in patients who have refractory anaemia and need regular transfusions which result in progressive iron accumulation, e.g. thalassemia major patients. According to D4 (page 238, section "Clinical Trials of Deferiprone"), clinical trials had shown that deferiprone was effective in the long term in most of the patients with transfusional iron overload. It generally decreased serum ferritin levels and hepatic iron concentrations (sections "Changes in Serum Ferritin Concentrations" and "Changes in Hepatic Iron Concentration"), standard indicators of iron accumulation.

Regarding the improvement in organ function, D4 focused particularly on the heart (page 239, section "Improvement in Organ Function"), noting that "*[b]ecause the leading cause of death in iron-loaded patients is cardiac iron loading, the ability to prevent and reverse cardiac iron loading is crucial for any iron chelator*". In that context, D4 referred to a clinical study of over one year where a patient with an established iron-related cardiomyopathy experienced a

reduction in cardiac stores and an improvement in cardiac function. The results were reported in reference 59, which is document D47 in these proceedings.

The patient in the clinical study of D47 had thalassemia intermedia and was treated with deferiprone at a dose of 75 mg/kg/day. The parties agreed that, unlike thalassemia major patients, thalassemia intermediate patients are not transfusion-dependent.

5.3 The appellant considered that the skilled person would have disregarded the teaching in D4 concerning the reduction of cardiac iron stores and improvement of cardiac disease reported in document D47 because it was unreliable. In D47, cardiac iron had been assessed by MR imaging, which at that time was not a validated method (D15a, paragraph below Figure 4 and D23, abstract and page 2178, section "Conclusions"). Furthermore, a closer look at the data in D47 showed that neither had cardiac iron stores been reduced nor cardiac function been improved.

The board disagrees. The appellant's reflections on the content of D47 and the skilled person's mindset are speculative. In the board's view, the skilled person would have considered the teaching in D47 credible for at least two reasons. Firstly, D47 is a peer-reviewed paper published in "Blood", a leading journal in the field of haematology. Second, as submitted by the appellant (letter dated 8 July 2020, paragraph 21), the lead author of D47, N.F. Olivieri, was a leading authority in the field at that time. Therefore the skilled person had no reason not to rely on the conclusions drawn by the authors of D47, in particular those on page 2747 that (emphasis added):

- the patient had "*evidence of* ***iron-related organ toxicity with*** *early hepatic cirrhosis and* ***mild cardiac diastolic dysfunction with lack of systolic increase with exercise***";
- L1 therapy reduced tissue iron load, as demonstrated by *inter alia* "***improvement in MRI of cardiac*** *and hepatic* ***iron***" (note that L1 is a synonym for deferiprone); and
- "*[o]ur report is the first to present evidence in humans for L1-induced* ***reduction of iron in the liver and heart***".

The authors of D4 also relied on D47 and the study disclosed therein, and therefore reported them in their review. As said study was carried out with a patient suffering from thalassemia intermedia, the board concludes that D4 does not specifically disclose the reduction of cardiac iron in transfusion-dependent patients.

5.4 Having regard to the difference in transfusion dependency between thalassemia intermedia and thalassemia major patients (see point 5.1, last sentence), the subject-matter of claim 1 differs from the teaching in D4 in that the patient having iron-induced cardiac disease is transfusion-dependent.

5.5 On the basis of this difference, the opposition division and the parties concurred that the objective technical problem to be solved could be formulated as the provision of an effective treatment of iron-induced cardiac disease in a transfusion-dependent thalassemia patient.

The board considers that such a formulation of the problem is incorrect because it anticipates the solution, namely the treatment of transfusion-dependent thalassemia patients (see Case Law of the Boards of Appeal, 9th edition, Chapter I.D.4.3.1). The board holds that the objective technical problem is rather the provision of an effective treatment for iron-induced cardiac disease with deferiprone in a further patient group.

This reformulation of the problem has no effect on the outcome of the assessment of inventive step since, regardless of which of the two versions is taken, the key issue is whether the skilled person might reasonably have expected deferiprone to be suitable for the treatment of transfusion-dependent thalassemia patients (see point 5.7 below).

5.6 The objective technical problem is solved by the use defined in claim 1, since the effective treatment of transfusion-dependent thalassemia patients having iron-induced cardiac disease is a functional feature of the claim. This is confirmed by the results of the clinical tests disclosed in the patent, which show (Table 2 and paragraphs [0076] and [0083]) that two out of five thalassemia major patients having a cardiac disease experienced an improvement in cardiac function when treated with deferiprone. The fact that cardiac function had improved upon iron chelation means that the cardiac disease was iron-induced.

For the sake of completeness, the board notes that the low statistical significance in Table 2 (P=1.000) refers to the comparison between deferiprone and desferrioxamine rather than to the improvement of cardiac disease.

Under these circumstances, there is no need to assess the post-published evidence in documents D22 and D50.

5.7 On the issue of obviousness, the parties were in dispute as to whether the skilled person, knowing that deferiprone was suitable for treating iron-induced cardiac disease in a thalassemia intermedia patient (D4), might reasonably have expected that a transfusion-dependent thalassemia patient having iron-induced cardiac disease could also be effectively and safely treated with deferiprone.

It was common ground that iron chelation in thalassemia major patients was more challenging than in thalassemia intermedia patients because the former are transfusion-dependent and receive considerably higher amounts of iron than the latter. It was also common ground that thalassemia major causes a greater accumulation of iron in the heart, while thalassemia intermedia does so preferentially in the liver (see also D44, page 500, right-hand column, lines 5-11).

However, as noted by the respondents, the cardiac disease in both the thalassemia intermedia patient in D4 and the transfusion-dependent thalassemia patient in claim 1 was caused by a cardiac iron overload. Thus in both cases reversal of the cardiac disease takes place by chelation of cardiac iron overload and prevention of further cardiac iron accumulation.

It is true that treatment of iron-induced cardiac disease in thalassemia major patients is generally more challenging than in thalassemia intermedia patients because the former are subjected to higher iron loads and because iron accumulates preferentially in the

heart. However, the nature of the treatment and the mode of action of deferiprone is identical in both situations: it removes iron excess by chelation. The difference between the two treatments is quantitative rather than qualitative: thalassemia major requires more extensive iron chelation to reverse the same iron-induced cardiac disease.

Thus, in assessing whether the skilled person might reasonably have expected that deferiprone could treat thalassemia major patients having iron-induced cardiac disease, it was relevant whether deferiprone might have been expected to cope with a quantitatively more challenging situation than the one in the closest prior art.

In this connection, the board notes that at the priority date the use of deferiprone as iron chelator in the treatment of thalassemia major was known and even approved in Europe as an alternative to the then-standard chelator desferrioxamine (see patent, paragraph [0006]). In particular, D4 (page 238, section "Clinical Trials of Deferiprone") reported that dose-response studies had shown that 75 mg/kg/day was the minimum dose required to achieve a negative iron balance in most patients with thalassemia major, and D9 reported that a group of 22 thalassemia major patients had been successfully treated with deferiprone at doses of between 75 and 120 mg/kg/day for over a decade. The patients did not develop any notable iron-induced cardiac disease.

Accordingly, at the priority date, it was known that:

- a dose of 75 mg/kg/day deferiprone could successfully remove cardiac iron overload in a thalassemia intermedia patient (D4);
- the same dose was the minimum for achieving a negative iron balance in most thalassemia major patients (D4); and
- doses of between 75 and 120 mg/kg/day could prevent, and even reverse, cardiac iron accumulation in thalassemia major patients (D4 and D9).

This knowledge was sufficient to give the skilled person reasonable expectations that deferiprone might successfully reverse iron-induced cardiac disease in a transfusion-dependent thalassemia patient.

Therefore the board concludes that the solution proposed in claim 1 was obvious and that it lacks inventive step within the meaning of Article 56 EPC.

5.8 The appellant focused its defence on the observation of cardiac damage associated with deferiprone treatment reported in several papers published in and after 1998. Those observations would have discouraged the skilled person from using deferiprone for treating thalassemia major patients, especially if they had a cardiac disease.

In the appellant's view, deferiprone had initially been regarded as a promising iron chelator for treating iron-induced cardiac diseases because it reduced serum ferritin (see D31, page 576, right-hand column, lines 6-10; D43) and liver iron concentrations (see D3, lines

5-6; D4, page 239, section "Changes in Hepatic Iron Concentration"), which were the standard indicators of cardiac iron at the time. However, serum ferritin and hepatic iron concentration are poor indicators of cardiac disease. This became evident in 1998, when a series of publications warned against the potential cardiac damage that deferiprone could cause in the long term (see D17, abstract 2184, last two sentences; D20, page 219, lines 1-2 and paragraph 3, and page 220, lines 12-17 and 28-31; D21, paragraph bridging pages 420 and 421; D46a, page 6, paragraph 2, last sentence; A6, summary, right-hand column, lines 7-11, and page 299, left-hand column, lines 4-8). Thus on the priority date the general opinion in the scientific community was that deferiprone was not suitable for treating iron-induced cardiac diseases and that it increased the risk of cardiac fibrosis. The skilled person would not have ignored these warnings, and would have refrained from using deferiprone to treat iron-induced cardiac diseases.

The publication of D9 in 2000 did not change this opinion. D9 had no weight because it was merely an abstract, its patients had no initial iron-induced cardiac disease, and the document did not report on the positive or negative impact of deferiprone on the heart. This was confirmed by D29 and D25, which showed that on the priority date the opinion that deferiprone was not suitable for treating iron-induced cardiac diseases prevailed.

5.9 The board disagrees. The appellant's argument is in line with the statement in the patent regarding the prior art (paragraph [0057]) that, although the long-term efficacy of deferiprone had been evaluated in various clinical trials, no information was available

on its long-term efficacy in preventing cardiac diseases or prolonging patient survival in patients having thalassemia major. Indeed, documents D17, D20, D21 and A6, all published in 1998, raised doubts as to the suitability of deferiprone for treating thalassemia major patients, and called for further evaluation.

However, document D9 was published in 2000, i.e. shortly before the priority date. It disclosed the results of a long-term clinical study which involved 22 thalassemia major patients who had been treated with deferiprone at a dose of 75-120 mg/kg/day for over a decade. The study was far longer than any of the studies in the other documents cited in these proceedings, and it certainly set aside the controversy raised by several publications in 1998 regarding the long-term use of deferiprone. The treatment in D9 proved effective in preventing cardiac damage and, although some side-effects occurred, none of the participants had to discontinue the therapy. The patients showed normal cardiac function: only two had a mild diastolic dysfunction. Thus, shortly before the priority date, D9 showed that long-term therapy of thalassemia major with deferiprone was effective and safe. The fact that D9 was an abstract was not a reason to consider its content unreliable. The fact that the patients in D9 had no iron-induced cardiac disease at the beginning of the study does not change the situation either, since the issue at stake is inventive step rather than novelty.

Regarding D29, the board does not consider relevant the passage cited by the appellant (page 651, left-hand column, lines 16-18) that "*there is good experimental evidence that compounds closely related to deferiprone can cause cardiac fibrosis in experimental animals*".

D29 is an excerpt from a textbook published shortly after the priority date, and may reflect common general knowledge before the priority date. However, the cited passage refers to compounds closely related to deferiprone and to tests in experimental animals, rather than to deferiprone itself and clinical tests. In addition, the context in which the passage is included discusses articles published in 1997 and 1998 and does not consider D9, published in 2000.

Regarding D25, Prof. Galanello stated (paragraph 5) that in 2001 a cardiac disease was an exclusion criterion for a clinical study involving deferiprone in combination with desferrioxamine. However, he specified neither the information considered by the ethical committee which established that criterion, nor how that information was assessed, nor the reasoning that led the committee to conclude that the available data did not support the efficacy of deferiprone in treating thalassemia patients with cardiac disease, while the prior art contained publications teaching the opposite. Hence document D25 does not demonstrate that on the priority date there was a prejudice against the use of deferiprone for treating iron-induced cardiac disease in thalassemia major patients.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated