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D E C I S I O N
of 26 April 2005

Case Number: T 0230/01 - 3.3.2

Application Number: 95943722.9

Publication Number: 0799037

IPC: A61K 31/44

Language of the proceedings: EN

Title of invention:

Methods and compositions for treating allergic rhinitis and other disorders using descarboethoxyloratadine

Applicant:

Sepracor Inc.

Opponent:

-

Headword:

Descarboethoxyloratadine/SEPRACOR

Relevant legal provisions:

EPC Art. 54, 56, 84, 97(1), 123(2)

Keyword:

"Main request and auxiliary request (1): novelty (yes) - use of a known medicament for the treatment of a specific allergic condition neither individualised nor specifically disclosed in the state of the art;"

"Inventive step (no) - a skilled person knowing the prior art had every reason to expect that the medicament would be useful in treating that specific allergic condition"

"Auxiliary request (2): novelty (yes) - vide supra"

"Inventive step (yes) - there is no hint or suggestion in the state of the art to treat that allergic condition at dosage levels which are significantly lower than what has been recommended in the state of the art for the treatment of allergic conditions using said known medicament"

Decisions cited:

G 0001/93, T 0077/87, T 0119/82, T 0591/90

Catchword:

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Case Number: T 0230/01 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 26 April 2005

Appellant: Sepracor Inc.
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Representative: Jump, Timothy John Simon
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 8 September 2000
refusing European application No. 95943722.9
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: J. Riolo
Members: G. F. E. Rampold
J. P. B. Seitz

Summary of Facts and Submissions

- I. The **appellant** is the **applicant** of European patent application No. 95 943 722.9 (the "application"), entitled "Methods and compositions for treating allergic rhinitis and other disorders using descarboethoxyloratadine". The appeal was filed on 7 November 2000 and lies against a decision of the examining division of the EPO pronounced at the close of the oral proceedings on 26 June 2000, with written reasons notified on 8 September 2000, by which the application was refused pursuant to Article 97(1) EPC.
- II. The decision under appeal was based on four amended sets of claims which were presented in the course of the oral proceedings before the examining division and formed the applicant's main request and its first, second and third auxiliary requests then on file.

Claim 1 of the **main request** read as follows:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treating allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount sufficient to provide a therapeutically effective amount of DCL or pharmaceutically acceptable salt thereof to a human."

Dependent claims 2 to 7 related to specific embodiments of the use according to claim 1.

Claim 1 of the **first auxiliary request** read as follows, with the amendments being highlighted in bold italics below:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount **sufficient to provide from 0.1 mg to less than 10 mg per day** of DCL or pharmaceutically acceptable salt thereof to a human."

Dependent claims 2 to 6 related to specific embodiments of the use according to claim 1.

Claim 1 of the **second auxiliary request** read as follows, with the amendments being highlighted in bold italics below:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount **sufficient to provide from 0.2 mg to 5 mg per day** of DCL or pharmaceutically acceptable salt thereof to a human."

Dependent claims 2 to 5 related to specific embodiments of the use according to claim 1.

Claim 1 of the **third auxiliary request** read as follows, with the amendments being highlighted in bold italics below:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in a treatment of allergic rhinitis in a human, while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines, said medicament to be administered in an amount **sufficient to provide from 0.2 mg to 1 mg per day** of DCL or pharmaceutically acceptable salt thereof to a human."

Dependent claims 2 to 5 related to specific embodiments of the use according to claim 1.

III. Of the numerous documents and other pieces of evidence presented in the course of the proceedings before the first instance and the subsequent appeal proceedings, the following are also referred to in this decision:

- (1) WO 85/037 07
- E1 Brandes et al, Journal of the National Cancer Institute, vol. 86, no.10, p.p 770-775 (May 1994)
- E2 Wiley et al, the Journal of Pediatrics, p.p. 799-802 (1992)
- E3 FDA Warning in JAMA vol. 268. No. 6, page 705 (1992)

- E4 Goodman and Gilman's, The Pharmacological Basis of Therapeutics, 9th edition, page 588 (1996)
- E5 A.P. Good et al, J. Cardiology, vol. 74, p 207 (July 1994)
- E8 Peer A Van et al, (Derwent abstract; accession No. 93-55671) Eur. J. Allergy Clin. Immunol. 48, suppl. 16, 34 (1993)
- E18 Goodman and Gilman's, The Pharmacological Basis of Therapeutics 8th Ed. (1990)

IV. In the decision under appeal, the examining division found that the claimed subject-matter in the main request and also in the auxiliary requests 1 to 3, although complying with the formal requirements of Articles 84 and 123(2) EPC and being novel within the meaning of Article 54(1) EPC, lacked an inventive step. The essence of the reasoning in the examining division's decision was as follows:

As acknowledged by the applicant in the introductory part of the description, at the priority date of the application it was already known that the compound **descarboethoxyloratadine** (hereinafter referred to as **DCL**) was the pharmacologically and orally active main metabolite of **loratidine**, and it was also already known that the parent compound **loratidine** itself was useful for the treatment of seasonal and perennial allergic rhinitis.

The examining division considered the disclosure in citation (1), relating to the antihistaminic properties of DCL and its proposed use in the treatment of allergic reactions in general, to represent the closest state of the art.

Given this closest state of the art, the examining division determined the problem to be solved as that of finding or choosing, within the general reference in citation (1) to the usefulness of DCL in the treatment of allergic reactions, a specific allergic condition which could successfully and efficiently be treated or cured using DCL as the therapeutic agent. The solution was the proposed use of DCL in the treatment of allergic rhinitis. The examining division concluded that it was *prima facie* obvious to try using DCL for the treatment of this specific allergic condition, in particular because efficacious treatment of allergic rhinitis with the structurally closely related antihistamine loratidine, which belonged to the same class of non-sedating piperidine antihistamines as DCL, was already known in the state of the art. In the view of the examining division, the assessment of inventive step was dependent on the answer to the question whether or not at the priority date of the application the alleged technical prejudice in fact existed in the art against using DCL for the proposed treatment of allergic rhinitis. It concluded that the evidence provided by the applicant was not sufficient for adequately substantiating the alleged prejudice and, consequently, that the claimed subject-matter in the main request did not involve an inventive step.

As regards the claimed subject-matter in the auxiliary requests, the examining division stated that citation (1) already recommended a low dosage regimen of 5 to 100 mg/day, preferably 10 to 20 mg/day, for the oral administration of DCL. It argued that it was the constant aim in the field of pharmacology and medicine

to try to reduce the dosage regimen for a given medicament to the minimum required level for the successful treatment of a particular condition or disease. The examining division concluded therefrom that it was routine work for the skilled practitioner and thus *a priori* not inventive to use the low doses of DCL indicated in claim 1 of the auxiliary requests, even if it was admitted by the examining division that at least in claim 1 of auxiliary request 3 the reduction of the proposed dosage to a regimen as low as 0.2 mg to 1 mg per day required for the treatment of allergic rhinitis was to be considered as being substantial.

- V. The appeal fee was paid on 7 November 2000 and the statement of grounds was filed with the appellant's letter of 18 January 2001. By its letter of 23 January 2004 to which the original of the declaration by Dr William W. Storms was attached, the appellant submitted further observations.
- VI. Oral proceedings before the board of appeal were held on 26 April 2005. With reference to the following features defined in general functional terms in claim 1 of all requests: *"while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines"* (see II above), the board raised at the beginning of the hearing certain serious objections under Article 84 EPC to the **clarity of claim 1** in all four requests then on file. In reply to the board's objections, the appellant asked for a break for deliberation. The appellant then requested to be given the opportunity to submit amended claims, if it arrived at the conclusion that this would

be useful and necessary to overcome the board's objections. This was allowed. After the break the appellant withdrew its initial requests that a patent be granted on the basis of the main request or one of the auxiliary requests before the examining division (see II above) and presented, instead, the following three requests:

The **main request** consists of a set of six claims, with claim 1 as the sole independent claim reading as follows:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treating allergic rhinitis in a human, said medicament to be administered in an amount sufficient to provide daily dose of 0.1 mg to less than 10 mg of DCL or pharmaceutically acceptable salt thereof to a human."

The **first auxiliary request (1)** consists of a set of five claims, with claim 1 as the sole independent claim reading as follows:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treating allergic rhinitis in a human, said medicament to be administered in an amount sufficient to provide daily dose of 0.1 mg to 5 mg of DCL or pharmaceutically acceptable salt thereof to a human."

The **second auxiliary request (2)** likewise consists of a set of five claims, with claim 1 as the sole independent claim reading as follows:

"1. Use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treating allergic rhinitis in a human, said medicament to be administered in an amount sufficient to provide daily dose of 0.2 mg to 1 mg of DCL or pharmaceutically acceptable salt thereof to a human."

VII. The arguments presented by the appellant in its written submissions and at the hearing before the board, insofar as these are still relevant to the claims in the current requests, can be summarised as follows:

The appellant made a series of critical observations concerning the examining division's finding that for the subject application, the closest prior art was represented by citation (1). In this respect, the appellant essentially argued that citation (1) disclosed the compound DCL (descarboxyethoxyloratadine) and showed that, in certain specific laboratory experiments, the compound DCL had an ability to inhibit histamine's capacity to induce paw edema in mice (see (1), page 6, line 29, to page 7, line 31). The citation suggested that these tests showed DCL to have antihistaminic properties (see (1), page 6, lines 24-29). The cited document also suggested that the compound could be used to treat allergic reactions in mammals (see (1), page 2, lines 4-8), but no information as to the nature of these allergic reactions and mammals was provided.

The appellant then recalled that for a compound to be effective in treating allergic rhinitis and other allergic conditions, it must be capable of selectively preventing histamine from binding to H₁ histamine receptors. Compounds with such a capacity were referred to as antihistamines or, more properly, as selective H₁ antagonists. However, at least two further types of histamine receptor, H₂ and H₃ receptors, were known to exist. Drugs which acted to selectively prevent histamine binding with these latter receptor types were known as selective H₂ and H₃ antagonists. Selective H₂ and H₃ antagonists were not capable of preventing histamine from binding H₁ receptors, and were not useful in the treatment of allergic conditions, including allergic rhinitis. At the priority date of the present application, those skilled in the art would have known that many H₃ antagonists have a capacity to reduce histamine-induced paw edema in mice. Those skilled in the art would also have known that a capacity to reduce histamine induced paw edema in mice was not necessarily indicative of antihistaminic activities of any description, as they would have known that other classes of drugs, including corticosteroids, were known to have such an effect.

The appellant also submitted that at the priority date of the present application, those skilled in the art of developing pharmaceutical products would not have considered the information given in (1) to have been sufficient for it to be concluded that DCL would have an inhibitory effect on allergic conditions, such as allergic rhinitis. Before drawing such a conclusion, such an individual would have considered it essential

for the compound to have been further characterised in one of the many pharmacological models known to be suitable for showing antiallergic activity,

In the pharmaceutical field, as argued by the appellant, expectation of mere efficacy was not enough; there must be a reasonable expectation that a putative medicine will be safe, before those skilled in the art would consider there to be a reasonable chance of succeeding with its development. Moreover, whilst a significant risk of an unpleasant side effect would be considered acceptable in the context of a drug shown to be effective in treating an otherwise fatal disease, such as cancer, even a slight risk of a harmful side effect would be unacceptable in a drug intended to treat a non-life threatening condition. Allergic rhinitis was very common, but it was certainly not life threatening. Therefore, when considering its therapy, those skilled in the art would view safety as being paramount. Even a slight risk of causing a potentially fatal side effect would be sufficient for them to decide against attempting to develop a particular active agent for this purpose.

In this context, the appellant submitted that at the priority date of the application, little was known about DCL itself, although it had been described as an active metabolite of loratadine and only differed from the latter by having a hydrogen atom in place of the ethoxycarbonyl group bound to the nitrogen atom in the piperidine ring of loratadine. At the priority date of the present application, loratadine was known to be an H₁ receptor antagonist, or antihistamine. It was also known that loratadine could be used to treat allergic

rhinitis, colds and chronic urticaria and that it had been suggested that it could be useful in treating other conditions, including allergic asthma, motion sickness, vertigo, cough and flu symptoms, and diabetic retinopathy (see the application, page 1, lines 13, to page 3, line 8). Loratadine was also known to be a member of a class of chemically and physiologically related antihistamines, referred to in standard text books as non-sedating piperidines. For example, in E18, which was considered to be a standard work in the field of pharmacology, loratadine was described, in the first column on page 587, as being a member of the class of piperidine H₁ antagonists. Although only one other member of the class, terfenadine, was mentioned in this passage, another member, astemizole, was identified as such, along with terfenadine, in table 3, on page 585 of this reference.

In view of the close relationship between DCL and loratadine, at the priority date of the present application, those skilled in the art would have expected DCL to share certain fundamental properties with loratadine and would have considered information relating to loratadine to be relevant to any consideration of DCL. Moreover, because they would be alert to the possibility that pharmacological effects can be common to a whole class of drugs, they would also have considered information concerning the other piperidine antihistamines to be of significance to DCL. However, although knowledge of the foregoing would have left a skilled person expecting DCL to be an H₁ antagonist, in view of the many uses that had been proposed for loratadine, he would not have had any reason to suppose that DCL would be effective in any

particular one of these, such as allergic rhinitis. Notwithstanding this, in view of its non-life threatening nature, a skilled person who did contemplate the use of DCL in the treatment of allergic rhinitis, would have been especially concerned by any reports of adverse reactions to any of these related drugs.

At the priority date of the present application, there had been reports and an official warning from the United States Food and Drug Administration of very serious cardiotoxic effects associated with the use of two members, terfenadine and astemizole, of the class of piperidine antihistamines, to which loratadine and DCL belong. These effects included ventricular arrhythmia, particularly torsades de pointes, cardiac arrest and even death. At least one of these reports and the official warning linked these effects together and gave the impression that they might be a class effect. For example E2 reported cardiotoxicity in children resulting from treatment with astemizole and included references to terfenadine having caused like side effects (see E2, page 800, second column and the abstract.) In E3, which is a warning issued by the United States Food and Drug Administration, it was stated that there were "risks of serious cardiovascular events in patients taking terfenadine" including "death, cardiac arrest, torsades de pointes, and other ventricular arrhythmias" and "serious adverse cardiovascular events in patients exceeding the recommended doses" including "torsades de pointes" at relatively low doses, with astemizole.

These two facts alone, as the appellant argued, would have meant that, at the priority date of the present application, a skilled person would have considered it possible for all of the compounds in the class of piperidine non-sedating antihistamines to share not only a desirable non-sedating antihistaminic effect, but also some seriously undesirable side effects.

Equally seriously, by the priority date of the present application, it had been reported in E1 that both loratadine and astemizole had been found to significantly promote the growth of tumors, specifically melanoma and fibrosarcoma. In E1, a correlation was reported between the rank order of potency of the antihistamines studied and the rank order of their capacity to enhance tumor growth (see E1, page 770, column 2, lines 24-28), and it was suggested that the more potent antihistamines, loratadine and astemizole, carried a greater risk of tumor promotion. As explained in greater detail on page 772 of E1, in the second paragraph of the results section, the tumor promotion activity of the various antihistamines was determined at dosage levels equivalent to those used in humans. Thus, in the assessment of tumor promotion activity described in E1, the more potent antihistamines were administered in smaller amounts than the less potent compounds.

The appellant concluded that on the basis of the foregoing analysis, those skilled in the art would have considered there to be a real risk of DCL causing side effects of a nature that would be considered unacceptable in a drug intended to treat a relatively trivial condition, such as allergic rhinitis, and that

there was a serious risk that the development of DCL for such a purpose, if initiated, would have to be aborted. Therefore, at the priority date of the application, skilled individuals would not have had a reasonable expectation of succeeding in the development of a product that included DCL as an active agent for the treatment of allergic rhinitis. The subject matter of claim 1, therefore, must involve an inventive step, as required by Articles 52(1) and 56 EPC.

With regard to the claims in the auxiliary requests, the appellant submitted that the low dose ranges for DCL recited in these claims were inventive. The skilled person would have been surprised that DCL could be efficacious in doses that either were at the lowest limit of the broad dosage ranges disclosed in (1) or were even lower than the lowest dosage suggested for DCL in citation (1) and the normal dosage of 10 mg suggested for loratidine.

VIII. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of either its main request filed during the oral proceedings or one of its two auxiliary requests also filed during the oral proceedings.

Reasons for the decision

1. The appeal is admissible.

Admissibility of the appellant's late filed requests

2. The board considers that the appellant's current main request and its first and second auxiliary requests, although presented only at the oral proceedings before the board, should be admitted into the proceedings. The appellant's assertion that these newly filed requests formed a response to the reservations and objections under Article 84 EPC, raised by the board at the beginning of a hearing to the clarity of claim 1 in all requests then on file, appears *prima facie* correct. The board therefore considers it justified to exercise its discretion in favour of the appellant, in spite of the late filing of the current requests.

The amended claims

3. The proposed amendments to claim 1 of all requests give rise to the question whether deletion of the functionally defined feature: *"while avoiding the concomitant liability of adverse side effects associated with the administration of non-sedating antihistamines"* from amended claim 1 of all requests and introduction, instead, of the recommended dosage regimen into these claims (see V above) is acceptable under Article 123(2) EPC.
 - 3.1 The aim of the claimed invention, as clearly expressed in lines 26 to 30 on page 7 of the application as originally filed (see International application No. PCT/US95/15995 published under the PCT as WO 96/20708), is the provision of *"a method of treating allergic rhinitis in a human while avoiding the concomitant*

liability of adverse side-effects associated with the administration of non-sedating antihistamines".

This aim is achieved in accordance with the disclosure in the application as originally filed by a method *"which comprises administering to said human a **therapeutically effective amount of DCL or a pharmaceutically acceptable salt thereof**"* (see page 7, lines 30-33).

What exactly is to be understood in the context of the claimed invention by a **therapeutically active amount** is explained, inter alia, on page 12, line 31 onwards: *"Thus the dosage range by the modes of administration described herein and for use in the methods of the present invention, are about 0.1 to less than about 10 mg per day. This is significantly lower than what has been recommended for other non-sedating antihistamines, including loratidine which has a recommended oral dose of 5 to 100 mg per day."*

This is further explained more precisely on page 14, line 11 onwards: *"In general, the total daily dose range, for the conditions described herein, is from about 0.1 mg to less than about 10 mg administered in single or divided doses orally, topically, transdermally, or locally by inhalation. For example, a preferred oral daily dose range should be from about 0.1 mg to about 5 mg. A more preferred oral dose is about 0.2 mg to about 1 mg.*

3.2 The board considers that deletion of the functionally defined feature in question, which merely relates to a

certain aim among others to be achieved by the claimed invention (while avoiding), and replacing this functional feature by the already originally disclosed technical means (ie the daily dose of DCL) that would enable the skilled person to achieve this particular aim, does not, in the present case, create subject-matter which extends beyond the content of the application as filed and, consequently, does not contravene Article 123(2) EPC.

3.3 Moreover, in the board's view, it follows from the description that the functional feature which has been deleted results from the administration of DCL at the recommended dose levels and does "not in itself provide a technical contribution to the subject-matter of the claimed invention". Therefore deletion of this feature does not affect the carrying out of the described invention, since it is not an essential part of it. Thus, in accordance with the principles underlying the interpretation of Article 123(2) EPC set out by the Enlarged Board in **G 1/93** (OJ EPO 1994,541), the board considers that, for this reason too, the removal from claim 1 of this functional feature, which did not modify the technical teaching and did not provide a technical contribution to the subject-matter of the claimed invention, does not contravene Article 123(2) EPC.

3.4 In view of the above, the amended claims in all three requests presented by the appellant at the hearing are considered as complying with the requirement of Article 123(2) EPC.

4. The claims as amended overcome the clarity objections raised by the board to the claims before the examining division (see V above).

The closest state of the art

5. The board agrees with the examining division's finding that citation (1) represents the closest and therefore the most relevant state of the art.

This citation discloses that the compound **DCL** (8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine), which is the decarboxylated product and the pharmacologically and orally active main metabolite of the H₁-antihistamine drug **loratidine** (8-chloro-6,11-dihydro-11-(1-ethoxycarbonyl-4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine), possesses **antihistaminic properties** with substantially no sedative properties at a clinically useful antihistaminic dosage (see especially page 6, last full paragraph to page 9, penultimate paragraph.)

The cited art (1) also discloses that the **antihistaminic properties** of DCL make this substance useful for treating **allergic reactions** in a mammal (see especially page 2, lines 4-7) and that a typical recommended dosage regimen is oral administration of **5 to 100 mg/day**, preferably **10 to 20 mg /day**, in two to four divided doses to achieve relief of the symptoms (see especially page 9, last paragraph).

- 5.1 Notwithstanding the above-mentioned clear and unequivocal disclosure of citation (1), the appellant

relied in writing and at the hearing before the board on the allegation that this citation was only superficially attractive as the closest prior-art document but was in fact speculative and did not provide sufficient and reliable information about the antihistaminic properties of DCL and its suggested use for the treatment of allergic conditions (see V above for more details).

With reference to the declaration by Dr William W. Storms, the appellant essentially submitted in support of its allegations that, in order for a compound to be effective in treating allergic rhinitis and other allergic conditions, it must be capable of selectively preventing histamine from binding to H₁ histamine receptors. According to the appellant's contentions, the experiments described in (1) based on the histamine-induced paw edema test would not have convinced the skilled reader that DCL is in fact a selective (H₁) receptor antagonist, in view of what was known about that particular test at the priority date of the application. Or, in other words, citation (1) would not have convinced those skilled in the art that DCL could effectively be used to treat allergic conditions, including allergic rhinitis.

- 5.2 In Article 54(2) EPC, "the state of the art" is clearly and unambiguously defined as "everything made available to the public by means of a written or oral description, by use, or in any other way before the date of filing of the European patent application". A document normally forms part of the state of the art, even if its disclosure is deficient, unless it can unequivocally be proven that the disclosure of the

document is not enabling, or that the literal disclosure of the document is manifestly erroneous and does not represent the intended technical reality. Such a non-enabling or erroneous disclosure should then not be considered part of the state of the art (see eg T 77/87, OJ EPO 1990, 280; T 591/90 of 11 December 1991).

5.3 The onus of proving the allegation that the disclosure of (1) is speculative, not reliable or does not represent the intended technical reality rests in the present case with the appellant. However, neither the appellant's submissions nor Dr Storm's declaration contain any convincing or objective evidence, let alone real proof, to support the appellant's contentions that the disclosure in (1), relating to DCL's capability of selectively preventing histamine from binding to H₁ histamine receptors, is indeed speculative, or that the skilled reader would have considered the information given in (1) to have been insufficient for it to be concluded that DCL does indeed have an inhibitory effect on allergic conditions.

5.4 Consequently, the disclosure of document (1), **as it stands**, is certainly to be taken into consideration as the closest and most relevant state of the art, when determining the problem to be solved and assessing novelty and inventive step.

Main request and first auxiliary request; the problem and its solution

6. Taking account of the closest prior art according to (1), the problem underlying claim 1 of the main request

and first auxiliary request in its broadest sense was to find or to choose, within the general reference in citation (1) to the usefulness of DCL in the treatment of allergic reactions by administering that medicament in a certain determined dosage to a mammal in need of it, a specific allergic condition which could successfully and efficiently be treated or cured using DCL as the therapeutic agent. The description of the application as originally filed suggests and indeed claims a series of allergic conditions and other diseases which can be treated with DCL: for example, allergic rhinitis in a human (page 7, line 27 to page 8, line 3; claims 1-7); retinopathy or other small vessel diseases associated with diabetes mellitus (page 8, lines 4-11; claims 15-21); cough, cold, cold-like, and/or flu symptoms and the discomfort, headache, pain, fever and general malaise associated therewith (page 8, lines 12-36; claims 22-40); symptomatic demographism in a human (claims 41-47); and allergic asthma in a human (page 9, lines 33-37, claims 8-14).

6.1 In view of the substantial limitation of the subject-matter of the claims in the course of the examination and subsequent appeal proceedings to the use of DCL in treating allergic rhinitis (see I and IV above), the solution of the problem proposed in claim 1 of the main request and the first auxiliary request was the use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of allergic rhinitis in a human.

6.2 From the description and examples disclosed in the present application, the board is satisfied that the problem is plausibly solved.

Novelty and inventive step

7. Having regard to the above, it is found that the state of the art according to citation (1) does not differ from the claimed use in claim 1 of the main request and first auxiliary request with regard to the medicament used (DCL or a pharmaceutically acceptable salt thereof) and that the recommended daily dosage ranges in citation (1) overlap with the claimed dosage ranges in the application (ie 5 to 100 mg/day, preferably 10 to 20 mg /day in citation (1) vs. 0.1 mg to less than 10 mg/day in claim 1 of the main request and 0.1 mg to 5 mg/day in claim 1 of the first auxiliary request). The sole difference between the state of the art according to citation (1) and the subject-matter of claim 1 in the above-mentioned requests consists thus in the **selection of allergic rhinitis** as the specific allergic condition to be treated from the reference in (1) to the usefulness of DCL or a pharmaceutically acceptable salt thereof for the treatment of allergic conditions in general by administering DCL to a patient in need of it.

7.1 The reference in (1) to the antihistaminic properties of DCL and its proposed use in the treatment of allergic reactions does not necessarily represent a disclosure, ruling out a selection from it of a specific allergic condition to be treated with DCL. Allergic rhinitis as the allergic condition or disease to be treated, which has been specifically singled out from the disclosure in (1) relating to the treatment of allergic reactions with DCL in general, has not yet been individualised or specifically disclosed in the

state of the art. The board thus agrees with the finding of the examining division that the subject-matter of claim 1, which is drawn up in the correct "second (further) medical use format", is new in accordance with the principles developed for establishing novelty in the EPO.

8. The allowability of claim 1 depends, therefore, on the answer to the question whether or not an inventive step was necessary to arrive at the claimed subject-matter when starting from the disclosure of citation (1).

8.1 As admitted by the appellant itself, long before the priority date of the application it was part of the common general knowledge that allergic rhinitis is a very common and widespread but relatively trivial allergic condition or disease. Moreover, prior to the priority date, the use and efficacy of the H₁-antihistamine drug loratidine, which is structurally closely related to DCL (see point 5 above), in treating seasonal allergic rhinitis was also already known (see application, page 2, lines 12-14). The skilled person, possessing this knowledge and being aware of the highly relevant teaching of citation (1) (see point 5 above), had every reason to expect that DCL would be useful and efficient in treating allergic rhinitis at a dosage level recommended in (1).

8.2 In the board's view, the cited state of the art pointed the notional skilled person in the direction of the claimed invention, and it only remained to confirm experimentally by a small number of routine tests that the thoroughly obvious result, namely the efficacy of DCL in the treatment of allergic rhinitis using the

claimed dosage regimen, was in fact obtained. However, the necessity of experimentally confirming a reasonably expected result cannot contribute to an inventive step. Thus, in the absence of any evidence showing that the selection of allergic rhinitis was unexpectedly associated with a beneficial effect, or a significant advantage or a worthwhile improvement in the broadest sense, the conclusion must be drawn that the claimed use of the DCL shows only predictable effects and is therefore obvious.

- 8.3 In its written submissions and during the oral proceedings, the appellant has cited a number of documents and reports, which have been published during the period between the publication date of citation (1) (29 August 1985) and the priority date of the present application (30 December 1994), and which supposedly prove a prejudice or a general trend in the art pointing away from the claimed invention.

An appellant who wishes to rely on a prejudice which might have diverted those skilled in the art away from the alleged invention has the onus of proving the existence of such prejudice (see T **119/82**, OJ EPO 1984, 217). However, in the board's judgment, there was no prejudice that might have prevented a skilled person from using DCL for the treatment of allergic rhinitis, nor has convincing evidence been brought of any such prejudice.

- 8.4 Thus, documents E2 and E3 report that two piperidine H₁ antagonists, terfenadine and astemizole, can cause cardiovascular side effects, such as cardiac arrests, torsades des pointes, and ventricular arrhythmias. The

- adverse effects of these drugs were due to accumulation of drug concentrations secondary to hepatic insufficiency, drug interactions, and substantial and acute overdosage. However, DCL as such, which is admittedly a known member of the class of piperidine H₁ antagonists, is not mentioned in E2 or E3.
- 8.5 Cardiotoxic side effects in one single patient were reported for loratidine in E5, whereby it remained uncertain whether these effects resulted from the administration of loratidine alone or from a drug interaction with quinidine. In this respect it should be noted that loratidine is still available as an Over The Counter (OTC) medicine to be sold without a prescription. Again, DCL as such is not mentioned in E5.
- 8.6 The **only reference to DCL itself** is contained in document E8, where it is mentioned that loratidine and DCL can interact with ketoconazole (KET) to give raised serum levels. However E8 refers to pharmacokinetic interactions and no mention is made in this document that raised serum levels of KET would be in any way associated with adverse side-effects resulting from the administration of either loratidine or DCL. Only the appellant made a cross-reference to E3 (no such reference is contained in E8) where it is said that raised serum levels of KET may precipitate the cardiotoxicity of fellow class member terfanidine.
- 8.7 Finally, document E1 reports that both loratidine and fellow class member astemizole can promote tumor growth in animals. Again, DCL as such is not mentioned in E1.

8.8 In sum, although there was a period of more than 10 years between the suggestion in (1) of using DCL for the treatment of allergic reactions in a mammal and the priority date of the application, the appellant did not succeed in providing any piece of evidence of a prejudice that might have prevented a skilled person from using the **substance DCL as such** for the treatment of allergic conditions. Moreover, loratidine, which is the structurally closest compound to DCL, is available up to now as an Over The Counter medicine for the treatment of allergic rhinitis. Thus from the evaluation of the evidence provided the conclusion must be drawn that the probative value of the cited documents and reports is insufficient to discharge the burden on the appellant of proving the alleged prejudice.

Second auxiliary request; the problem and its solution

9. Starting again from citation (1) as the closest prior art, the problem underlying claim 1 of the second auxiliary request is different from that underlying claim 1 of the main and first auxiliary requests. The problem here was to find a worthwhile improvement of the known method for treating allergic reactions in a mammal using DCL as the medicament.

9.1 The solution of this problem was the proposed use of DCL, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating allergic rhinitis in a human, said medicament to be administered in an amount sufficient to provide **the extremely low daily dose** of 0.2 mg to 1 mg of DCL or a pharmaceutically acceptable salt thereof to a human.

9.2 From the description and examples disclosed in the present application, and, moreover, in the absence of any evidence to the contrary, the board is satisfied that the problem is plausibly solved. It is evident to a person skilled in the art that utilising DCL at the recommended low dose levels is advantageous since it results in clearer dose-related definitions and efficacy, diminished adverse side-effects, and accordingly, an improved therapeutic index (see application page 13, lines 10-13) and avoids dangerous overdoses.

Novelty and inventive step

10. Apart from the selection of allergic rhinitis as the allergic condition to be treated (see 7, 7.1 above), the claimed use in claim 1 of the second auxiliary request additionally differs from the disclosure of citation (1) by the recommended daily dose of 0.2 mg to 1 mg of DCL or a pharmaceutically acceptable salt thereof. Novelty is therefore beyond any doubt.

11. For the person skilled in the art, at least two steps were necessary in order to arrive at the solution as claimed. Citation (1) teaches that the **preferred** recommended dosage regimen is 10 to 20 mg/day for oral administration of DCL of (see end of page 9). Even if the skilled person in a first step considered lowering the preferred recommended dosage regimen in (1), there is not the slightest hint or suggestion in the cited prior art that a **daily dose as low as 0.2 mg to 1 mg of DCL** or a pharmaceutically acceptable salt thereof would

indeed be sufficient for the efficacious treatment of any allergic condition.

The second step was then to find a particular allergic condition which could be efficaciously and successfully treated using the extremely low dosage regimen recommended in claim 1. There is again not the slightest hint or suggestion in the cited prior art that it is allergic rhinitis which could be successfully treated with DCL at dose levels that are so significantly lower than what has been recommended in the cited state of the art for the treatment of allergic conditions using either DCL or loratidine.

11.1 In sum, the board does not share the opinion of the opposition division in the decision under appeal that constant practice in the pharmaceutical industry and research would have provided a strong incentive for the skilled person to try treatment of allergic rhinitis using DCL at a dosage which is substantially below the minimum dosage regimen recommended in (1) for the treatment of allergic conditions.

11.2 In view of the foregoing, the board is convinced that the subject-matter of the second auxiliary request also meets the requirement of inventive step in accordance with Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant a patent on the basis of claims 1 to 5 of auxiliary request 2 filed during the oral proceedings, provided the description is correctly adapted.

The Registrar:

The Chairman:

A. Townend

J. Riolo