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D E C I S I O N
of 18 January 2001

Case Number: T 1009/97 - 3.3.2

Application Number: 91900414.3

Publication Number: 0502092

IPC: A61K 9/22

Language of the proceedings: EN

Title of invention:
Oral composition for the treatment of inflammatory bowel diseases

Patentee:
Aktiebolaget Draco

Opponents:
Dr Falk Pharma GmbH
Farmaceutisk Laboraturium Ferring A/S

Headword:
Oral budesonide/ABO DRACO

Relevant legal provisions:
EPC Art. 54, 56, 84, 114, 123(2), (3)

Keyword:
"Admissibility of the opposition of opponent II: yes"
"Admissibility of late-filed claims and expert declarations: yes"
"Unproven allegation that the disclosure in the closest state of the art was erroneous or not reliable"
"Novelty: yes"
"No implicit disclosure in the state of the art"
"Inventive step: no"
"Second or further medical use obvious in view of the known use of budesonide"

Decisions cited:
T 0219/83, T 0077/87, T 0591/90, T 0838/92

Headnote:

The question of whether or not a representative, who acted in certain issues concerning the patent in suit for both the proprietor (appellant) and the opponent (respondent), filed the opposition in breach of the rules of professional conduct or mutual contractual obligations is relevant only to the internal relationship between the clients and their representative, and has no bearing on the opposition or opposition appeal proceedings.

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Case Number: T 1009/97 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 18 January 2001

Appellant: (Proprietor of the patent)
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Respondent II: (Opponent II)
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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 25 July 1997 revoking European patent No. 0 502 092 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
S. Hoffmann

Summary of Facts and Submissions

I. The appellant is proprietor of European patent No. 0 502 092 (application No. 91 900 414.39).

II. Notices of opposition were filed independently by respondent (opponent) I and respondent (opponent) II. Both requested revocation of the patent under Article 100(a) EPC on the grounds of lack of novelty and inventive step; under Article 100(b) EPC because of insufficiency of disclosure; and under Article 100(c) EPC because of inadmissible extension of its subject-matter. The grounds of opposition under Article 100(a) EPC were supported, *inter alia*, by the following citations:

(1) H. Malchow et al, "Therapie des Morbus Crohn", published in Dtsch. med. Wschr. 109, pp. 1811-1816, 1984

(4) D. P. Jewell, "Corticosteroids in the Management of Ulcerative Colitis and Crohn's Disease", published in Gastroenterology Clinics of North America, Vol. 18, No. 1, pp. 21-34, March 1989

(8) A. Danielsson et al, "A Controlled Randomized Trial of Budesonide versus Prednisolone Retention Enema in Active Distal Ulcerative Colitis", published in Scan. J. Gastroenterology, Vol. 22, pp. 987-992, 1987

(9) S. L. Wolman, "Use of Oral Budesonide in a Patient with Small Bowel Crohn's Disease and Previous Pseudotumor Cerebri Secondary to Steroids", published in Scan. J. Gastroenterology, Vol. 24,

Suppl. 158, pp. 146-147, 1989

(12) EP-A-0 040 590.

III. With his reply to the notices of opposition, the appellant (proprietor) provided, *inter alia*, evidence that, due to a merger of two formerly independent law firms, the professional representatives acting for opponent II seemed to share identity, or at least were closely associated with the representatives who handled for the parent company of the appellant (proprietor) the Danish national phase of the patent in suit and other patents which were closely related to the subject-matter of the present patent. This being the case, the proprietor concluded that the representatives, who had filed opponent II's opposition, were not entitled to act against him and objected to the admissibility of the opposition and the status of opponent II as a party to the proceedings.

IV. The patent was revoked. The stated ground for the revocation of the patent was lack of novelty of the main request and lack of inventive step of the auxiliary request. The essence of the reasoning in the decision to revoke the patent was as follows:

- The decision, as to whether or not a duly authorized professional representative acted before the EPO in breach of his professional duties or internal contractual obligations did not lie within the competence of the opposition division. It was therefore not in a position to accept the proprietor's objections to the admissibility of the opposition lodged by opponent II and to opponent II’s procedural

status.

- Neither of the notices of opposition contained any indication of facts, evidence or arguments related to the grounds of opposition set out in Article 100(b) and (c) EPC. Consequently, the unsubstantiated grounds had to be considered as non-existent in the notices of opposition.

- As to the grounds of opposition laid down in Article 100(a) EPC, the opposition division considered citation (9) to be the closest state of the art. This citation referred to the use of oral budesonide in the treatment of a patient with small bowel Crohn's disease. The disclosure of citation (9) included, in the opinion of the opposition division, the administration of budesonide as relapse preventing treatment of Crohn's disease in the small intestine and was accordingly prejudicial to the novelty of the main request.

- Concerning the auxiliary request, the opposition division did not call into question that the specific formulation used for oral administration of budesonide conferred novelty on the subject-matter of the claims. It concluded, however, that citation (9) suggested for the treatment of Crohn's disease the use of a controlled release formulation which released its budesonide content in sufficient concentration in that part of the intestine where the disease resided to exert its local topic action. Since citation (12) disclosed suitable formulation techniques to provide oral compositions of budesonide fulfilling all

requirements of controlled release, the subject-matter of the auxiliary request was, in the judgment of the opposition division, the result of an obvious combination of the teachings of citations (9) and (12).

V. The proprietor of the patent filed an appeal against this decision. Replies to the statement of grounds of appeal were filed by both respondent I, together with a declaration of Professor Schölmerich (expert in gastroenterology), and respondent II. An oral hearing was scheduled to take place on 18 January 2001. In a faxed letter dated 15 January 2001, respondent II confirmed that he had decided to take no further part in the opposition proceedings.

VI. About one month in advance of the oral proceedings, the appellant filed a new main request and two auxiliary requests and cancelled all previously filed requests. These new requests were accompanied by declarations by the three Professors Hermon-Taylor, Hodgson and Rutgeerts (all experts in gastroenterology), and one by Dr Persson (expert in clinical statistics). Independent claims 1 to 3 of the main request for the designated states, except ES and GR, are worded as follows:

"1. Use of budesonide, or the 22 epimer thereof, in the preparation of a pharmaceutical composition for the treatment by the oral route of Crohn's disease in the small intestine as relapse preventing treatment.

2. Use of budesonide, or the 22 epimer thereof, in the preparation of a pharmaceutical composition for the treatment by the oral route of Crohn's

colitis in its active phase.

3. Use of budesonide, or the 22 epimer thereof, in the preparation of a pharmaceutical composition for the treatment by the oral route of Crohn's colitis in its chronic phase as relapse preventing treatment."

Claims 1 to 3 of the first auxiliary request differ from the corresponding claims of the main request by the addition of the following specification at the end of each claim: "wherein in said treatment the glucocorticosteroid exerts its action locally on the bowel".

Claims 1 to 3 of the second auxiliary request differ from the corresponding claims of the main request by the addition of the following specification at the end of each claim: "said pharmaceutical composition being a multiple unit composition in a capsule wherein the units which contain the glucocorticosteroid are enteric and/or slow release coated."

VII. The appellant’s arguments submitted in writing and during the oral proceedings can be summarised as follows:

- In view of the decision of respondent II to take no further part in the opposition proceedings, the appellant, for his part, did not pursue the status of respondent II’s participation in the present proceedings any further.

- The decision of the opposition division was based on the prior art of citation (9), which was not a

reliable document. (9) was concerned with the clinical condition of one single patient. Prior to the administration of budesonide, this patient was subjected to a number of other treatments. It was therefore not at all certain that any improvement achieved was the result of treatment with budesonide as opposed to a late or lingering effect from another treatment.

- Moreover, Crohn's disease was a complex medical condition which exhibited many different symptoms. Since the author of (9) essentially concentrated on the presence or absence of pain, and pain possibly originated from other sources of the patient's condition, it was likewise not certain that the treatment with budesonide in (9) truly resulted in any improvement of the patient's Crohn's disease syndromes.

- Citation (9) itself made no claim to have effected relapse prevention treatment in the small intestine. Even if one were to accept that (9) disclosed some kind of treatment of some kind of Crohn's condition, it was manifestly not Crohn's colitis in its active or chronic phase as in presently effective claims 2 and 3. Even in so far as the claims concern Crohn's disease in the small intestine, it was certainly not clearly and unambiguously derivable that by the treatment disclosed in (9) relapse prevention was achieved, or even attempted. The patient's condition was not monitored for anything like long enough for a clear conclusion to be drawn to the effect that relapse prevention had indeed occurred.

- The appellant's statements regarding the substantial deficiencies in the disclosure of citation (9) were, in his opinion, fully supported by the first three Declarants who all were experts and practising clinicians in the field of gastroenterology in general and Crohn's disease in particular.

- In view of the foregoing, the claims of the main request were novel because citation (9) failed to provide clearly and unambiguously their subject-matter. If the board disagreed with that, (9) failed to provide the subject-matter of the auxiliary requests' claims in a clear and unambiguous manner.

- The skilled person scrutinising the teaching of (9) would not select this citation as the closest state of the art and as his starting point for arriving at the claimed invention. The above-mentioned deficiencies in (9) would lead the skilled person to be very sceptical indeed about following or developing the teaching of (9).

- In contrast to (9), a skilled person would rather regard the section of citation (4) concerning the treatment of active Crohn's disease with prednisolone as a trustworthy and meaningful disclosure. He could sensibly begin to consider how to develop further treatments for Crohn's disease, possibly by using other steroids. At the priority date it was unclear whether steroids acted mainly locally or mainly systemically for Crohn's disease. Since there was considerable doubt over this, budesonide was plainly a poor

choice if a systemic effect was required. The skilled person would therefore have turned to steroids other than budesonide on the basis of (4) for the treatment of Crohn's disease. Moreover, in view of the disclosure in (4) the skilled person would not consider it realistic to use budesonide, or any other steroid, to maintain remission or effect relapse prevention treatment as presently claimed.

- In view of the above, the appellant concluded that the subject-matter claimed in the patent in suit was in no way obviously derivable from any of the cited documents taken either individually or in combination.

VIII. The respondents' submissions both in the written procedure and at the oral proceedings can be summarised as follows:

- The appellant's requests and the accompanying declarations were filed late and should therefore not be admitted into the proceedings. In particular, the admission of the declarations would result in a disadvantage to the respondent, because of lack of time for filing a written reply in the short period between the date of filing of the declarations and the date of the oral proceedings.

- The specification added to claims 1 to 3 of the first auxiliary request ["wherein in said treatment the glucocorticosteroid exerts its action locally on the bowel"] was inadequately supported by the originally filed documents and

therefore not acceptable under the terms of Article 123(2) EPC.

- Citation (9) disclosed clearly the use of budesonide as a relapse preventing treatment by the oral route of Crohn's disease in the small intestine. In sharp contrast to the patent in suit, which totally failed to provide any clinical trials or clinical data to support the effectiveness of the claimed treatment of the various conditions of Crohn's disease, citation (9) described exactly the entire course of the patient's treatment of Crohn's disease, the full range of the patient's clinical data and provided clear evidence of the effect of budesonide achieved in this patient. As Professor Schölmerich confirmed, the scientific correctness and reliability of the clinical data and results disclosed in (9) were for the skilled person beyond all shadow of doubt.

The content of (9) was therefore clearly prejudicial to the novelty of the claimed use of budesonide as relapse prevention treatment of Crohn's disease in the small intestine.

- The distinction in the independent claims of the patent in suit between treatment of small bowel Crohn's disease and Crohn's colitis was a purely artificial one. A therapy which was effective in a certain condition of Crohn's disease was known to be effective in the treatment of other Crohn's conditions as well. If the board nevertheless considered acknowledging the novelty of the claims relating to the treatment of Crohn's colitis, such

claims would not involve an inventive step.

- For the person skilled in the art, knowing from (9) that orally delivered budesonide was effective in the treatment of ileal Crohn's disease, it was plainly obvious to use budesonide for other conditions of Crohn's disease as well.

- That budesonide exerts its action in the intestine locally rather than systemically was already known from several publications, for example citations (4) and (9). Consequently, the task of the skilled person was to find a suitable formulation which released its budesonide content in that part of the intestine where the disease resided. Since appropriate formulations for the treatment of Morbus Crohn meeting the above requirements were already known from (12), the subject-matter of the claims of the first and secondary auxiliary requests did not involve an inventive step either.

IX. The appellant requests that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of the main request or the first or second auxiliary request, all filed on 18 December 2000.

Both respondents request that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. The question of whether or not the representatives who

filed the opposition for respondent II acted in breach of the rules of professional conduct or mutual contractual obligations is relevant only to the internal relationship between the appellant and his representatives, and has no bearing on the present opposition and opposition appeal proceedings.

2.1 Even if the filing of the opposition by representatives, who apparently acted in certain issues concerning the patent in suit for both the appellant and respondent II (see for more details paragraph III above), was based on the alleged breach of the professional code or any internal contractual obligations, nothing in the EPC would either oblige or enable the board to adjudicate this issue. Nor would the EPC give the board of appeal power to declare the status of the opposition invalid and to exclude respondent II as a party from the ongoing proceedings, if the opposition was indeed filed in breach of the rules of professional conduct or contractual obligations by which the representatives in the internal relationship with the appellant were bound (see in this respect: decision T 838/92 of 10 January 1995).

2.2 The board concurs with the conclusions of the opposition division concerning the admissibility of the opposition lodged by respondent II and his status as a party to the first-instance opposition proceedings. Article 107 EPC states that where one party filed an appeal, any other parties to the first-instance proceedings are parties to the appeal proceedings as of right. Consequently, respondent II remains party to the appeal proceedings pursuant to Article 107 EPC, irrespective of his declaration to take no further part

in the opposition proceedings.

3. By cancellation of the formulation claims the patent's subject-matter has been narrowed considerably to contain in all three current requests only claims in the second medical use format. The latter are based on claims 18 to 22 and 19 to 22 in the application as filed and the patent as granted respectively.

3.1 The claims in all three requests were amended with the aim of reducing the claimed subject-matter to one specific embodiment of the application as filed and the patent as granted and achieving a better delimitation from the state of the art cited in the proceedings. Consequently, the amendments mentioned above did not change the particular purpose and character of the claimed invention as set out in the application as filed and therefore, did not prevent the present case from being ready for the final decision at the conclusion of the oral proceedings. Further, all amendments can fairly be said to be occasioned by grounds for opposition specified in Article 100(a) EPC and are therefore admissible under the terms of Rule 57a EPC. Moreover, the period of one month between the date of filing of the present requests and the date of the oral proceedings was sufficient to give the other parties and the board the opportunity to study the amended requests. In the circumstances of the case the board decided during the oral proceedings to admit the main, first and second auxiliary requests for their consideration.

3.2 By filing the declarations of Professors Hermon-Taylor, Hodgson and Rutgeerts, the appellant apparently sought to react and reply to the submissions and arguments in

the declaration of Professor Schölmerich filed by respondent I with his observations presented in response to the appellant's statement of grounds. Moreover, the board considers that the said declarations were referred to by the appellant as expert opinions in support of his arguments and that, as such, they are not citations which, under Article 114(2) EPC, could be rejected as being late. Therefore, in the board's judgment, the declarations in question to which the appellant refers in support of his arguments should be regarded as part of theses arguments and should not be rejected as being filed late.

3.3 As regards the admissibility of the declaration of Dr Persson into the proceedings, the board takes the following view. In his observations presented in response to the appellant's statement of grounds, respondent I has maintained his objections to the lack of clinical trials and clinical data in the patent in suit and has, accordingly, contested the effectiveness of the claimed use of budesonide in the treatment of the particular conditions of Crohn's disease specified in the claims. The burden of proving this allegation would be in the present case with the respondent (opponent) I.

In a case such as the present, where an opponent disputes in the first and, subsequently, second instance the correctness of certain results in the patent in suit and, accordingly, the existence of an inventive step, he has to expect at any stage of the proceedings that the proprietor of the patent in suit will file counter-evidence to support his claim and to counter the respondent's prevailing allegations. Even

if the respondent himself had not filed by that date his own evidence in support of his allegation, he could not really have been surprised that the appellant filed suitable counter-evidence in the form of Dr Persson's declaration in advance of the oral proceedings. In view of the preceding considerations and in the circumstances of the case, the board considered the period of one month sufficient to study the declaration and decided within its discretion under Article 114(2) EPO to admit it into the proceedings.

4. The claims in the present main request and second auxiliary request are all adequately supported by the originally filed documents. Since this has not been contested, there is no need to expand in detail on this matter.

4.1 Contrary to the assertions of respondent I during the oral proceedings, the above conclusion applies equally to the claims of the first auxiliary request. The references below to support for the amendments in the current version of the claims according to the first auxiliary request are to the International application published under the PCT (WO 91/07172). As to the additional specification in claims 1 to 3 that "the glucocorticosteroid, ie budesonide, exerts its action locally on the bowel", this is either directly taken from or implied by and therefore derived from the disclosure in the first two full paragraphs on page 8 (see especially lines 21 to 25). The distinction between the local action of budesonide either in the small intestine (claim 1) or in the large intestine, specifically in the colon, (claims 2, 3) is further based on the statements in lines 11 to 16 on page 8.

4.2 The amended claims therefore comply with Article 123(2) EPC. An infringement of Article 84 EPC resulting from the amendments effected in the claims according to the appellant's present requests is similarly not recognisable.

4.3 The amendments narrow the scope of protection conferred in comparison with the claims as granted. Thus, no objection under Article 123(3) EPC arises against the current claims either.

5. For an objective assessment of the technical problem to be solved, it is established legal practice in the EPO to determine the closest prior art to the claimed invention.

5.1 Citation (9) describes the course of treatment of a patient, who was diagnosed as having "terminal ileal" Crohn's disease, and the effect of orally delivered budesonide in the treatment of this patient. The author of (9), Dr Wolman, is undoubtedly a recognised practising clinician having comprehensive experience and expertise in the field of gastroenterology. This has not been contested and is moreover supported by his declaration submitted with respondent II's letter during the opposition proceedings on 9 June 1997. In this capacity, Dr Wolman reports in citation (9) the course of the patient's medical treatment on the basis of the following clinical data in chronological order:

- diagnosis by repeated X-rays revealed recurrence of acute terminal ileal Crohn's disease in a patient, six month after she had been treated for the same disease by surgery to remove the afflicted area of the small bowel (terminal ileal

resection);

- treatment with a variety of medications including oral and intravenous metronidazol and 5-ASA (Pentasa, 5-aminosalicylic acid), as well as the general precaution of keeping the patient NPO (nil per os), were ineffective;

- symptoms subsequently developed to a stage at which the bowel became obstructed; this resolved with NG suction and IV fluids; the reinstitution of food again produced abdominal pain;

- on this occasion she was kept NPO (nil per os) and was started on a course of budesonide capsules, as the sole medication,

- after a further four days on this medication, feeding was reinstituted with clear fluids and then full diet and the patient did well for 3 months;

- reduction of budesonide from a regimen of 10 x 0.5 mg caps/day to 8 caps/day resulted in recurrent pain but resolved on returning to 10 caps/day;

- after 3 months of treatment at a regimen of budesonide of 5 mg/day no systemic side effects of steroids occurred.

By monitoring the patient's condition and evaluating in detail the collected clinical data, Dr. Wolman reaches in (9) the following express conclusions: "Budesonide 5 mg/day is effective in the treatment of ileal Crohn's

disease" and "Budesonide shows great potential for the treatment of ileal Crohn's disease without steroid side effects" (see (9), end of page 147).

5.2 The appellant himself has unequivocally acknowledged by reference to citation (9) in the application as published (see page 5, lines 27 to 29) and the patent as granted (see pages 41 to 44) that "the use of oral budesonide in the treatment of small bowel Crohn's disease in its active phase has been described" before the priority date of the patent in suit. This indicates, in the board's judgment, that the appellant's own experts had originally no reasoned doubts on the correctness of Dr Wolman's conclusions.

Similarly, the opposition division in its decision and both respondents in their submissions considered the content of citation (9) to be the closest state of the art in relation to the claimed use of budesonide in the patent in suit.

5.3 Notwithstanding the above, in the course of the opposition and appeal proceedings the appellant relied on the allegation that the Wolman paper (9) was only superficially attractive as the closest prior-art document but was in fact not a reliable document because of its many deficiencies. In support of his allegation that Dr Wolman's conclusions in (9) were erroneous or not reliable, the appellant submitted during the appeal proceedings declarations by Professor Hermon-Taylor, Professor Hodgson and Professor Rutgeerts. The board notes that all three refer from a scientific point of view to certain deficiencies in the disclosure of citation (9).

5.4 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).

The onus of proving the allegation that the disclosure of (9) is erroneous, not reliable or does not represent the intended technical reality rests in the present case with the appellant (proprietor).

5.5 The board has carefully taken into consideration every single point of criticism in the evaluation of the disclosure of (9) in the above-mentioned three declarations and the conclusions drawn therefrom. The criticism of the disclosure in the Wolman paper appears to focus primarily on the following points:

- citation (9) was concerned with the clinical condition of a single patient; a person skilled in the art of the management of Crohn's disease would know that it is not possible to base Dr Wolman's conclusion on the single case with its associated uncertainties, disclosed in the abstract (see eg Hermon-Taylor, paragraph 11);

- no attempt to asses the patient's condition using the CDAI (Crohn's Disease Activity Index) was reported; pain, when considered in isolation, was not a reliable indicator of Crohn's disease severity (see eg Hodgson, paragraphs 9, 21 to 23; Rutgeerts, paragraphs 5 to 8; Hermon-Taylor, paragraphs 11 to 13);

- the treatment with budesonide was a double "non-blind" or "open" one (see eg Rutgeerts, paragraph 10; Hodgson, paragraph 22);

- citation (9) was accepted as an un-refereed paper without scientific scrutiny (see eg Hodgson, paragraphs 6 to 9);

- (9) provided no evidence that the active small bowel Crohn's disease in the patient was effectively treated by the budesonide therapy and it provides no details of the nature of the composition used (see eg Hodgson, paragraph 27, Rutgeerts, paragraph 13);

- (9) provided no evidence that the patient's improvement observed was actually the result of the treatment with budesonide, as opposed to a late or lingering effect from any other therapy undergone by the patient in the course of her treatment reported in (9) (see eg Hodgson, paragraphs 12-15; 18, 19, Hermon-Taylor, paragraph 13);

- Dr Wolman's conclusion was only one possible deduction from the limited clinical data (see eg Hermon-Taylor, paragraphs 11, 13).

5.6 However, neither the appellant's submissions nor the expert's declarations contain any convincing or objective evidence, let alone real proof, to show in an unequivocal manner that the disease treated in (9) was indeed not Crohn's disease, or that the clinical data were indeed incorrectly interpreted, or that the patient's improvement was indeed not the result of her treatment with orally delivered budesonide, and, in particular, that Dr Wolman's express conclusions at the end of (9) were erroneous or not reliable.

In this respect, the board must give the same weight to Professor Schölmerich's declaration submitted by respondent I and his submissions during oral proceedings. According to Professor Schölmerich's expert opinion, the scientific correctness of the clinical data and results reported by Dr Wolman in (9) was beyond doubt (see Schölmerich: section 3, end of paragraph 4) and, on the basis of the clinical data provided in (9), the improvement in the patient's condition was the logical consequence of her treatment with orally delivered budesonide.

The board has no doubts at all on the outstanding scientific and professional qualifications of the Declarants leading them to their personal and subjective evaluation of the teaching in (9). However, in the absence of any objective evidence and real proof, the Declarants' personal evaluations of document (9) and their subjective opinions are clearly insufficient to prove in an unequivocal manner that the essential facts reported in (9) and the conclusions drawn by Dr Wolman were in fact erroneous or not reliable.

Consequently, document (9), as it stands, is certainly to be taken into consideration when determining the problem to be solved and assessing novelty and inventive step.

5.7 Citation (4) is a review paper relating to the use of corticosteroid compounds in the management of ulcerative colitis and Crohn's disease. The section of citation (4) specifically relating to Crohn's disease (see especially end of page 28 onwards) refers to two studies concerning the treatment of Crohn's disease in its active phase with orally delivered corticosteroid compounds. The National Cooperative Crohn's Disease Study (NCCDS), which was carried out in the USA and used the corticosteroid **prednisolone** in a dose that varied according to the severity of the disease from 0.25 mg/kg to 0.75 mg/kg, showed the benefit to be mainly for ileal disease. The European Cooperative Crohn's Disease Study (ECCDS) used the analogous corticosteroid compound **6-methylprednisolone** (28 mg/day reducing to 12 mg per day over 6 weeks). This treatment is reported in (4) to be effective for all disease locations (ileal or colonic).

5.8 In view of the preceding considerations, the board considers, in accordance with the opinion of the respondents and the opposition division, that the disclosure of (9) represents the closest state of the art.

6. Before defining the problem and reaching a decision on the patentability of the claimed subject-matter in the patent in suit, consideration must be given to the respondents' contention that the distinction between the different conditions of Crohn's disease made in

present claims 1 to 3 is essentially artificial and arbitrary.

6.1 The board is fully aware of the fact that certain conditions of Crohn's disease may occur simultaneously in different sections of the digestive tract, for example, the ileum and the colon (see eg (1): especially Fig 1, page 1812; page 1814, right hand column, "Ileokolitis) and that the border between Crohn's conditions may be fluid in certain cases. However, the location of Crohn's disease solely in a specific section of the gastrointestinal tract is well documented in the cited state of the art. As an example only, the patient in (9) was clearly diagnosed as having terminal ileal Crohn's disease. Further, in (1) and (4) a clear distinction is made between the location of the disease in the small intestine on the one hand, ie duodenum, ileum (see eg (1): page 1814, right hand column, 3rd full paragraph; (4): page 29, line 6, of the text portion, "mainly for ileal disease") and in the large intestine, ie colon, on the other (see (1): page 1814, right hand column, last paragraph; (4): page 29, line 9 of the text portion "ileal **or** colon").

6.2 Similarly, the distinction made between the treatment of Crohn's disease in its active phase, on the one hand, and relapse prevention or maintenance treatment, on the other, is derivable, for example, from document (4). Thus, on page 29 of (4) reference is made to the fact that the glucocorticosteroid compounds prednisolone and 6-methylprednisolone were mainly effective in the treatment of ileal disease or all disease locations, but essentially failed to maintain remission.

6.3 Furthermore, Professor Rutgeerts explained during the oral proceedings, to the board's satisfaction, that in each patient a careful diagnosis of the location and severity of Crohn's disease has to be made and that the clinical symptomatology and the methods of treatment of each of the different conditions vary strikingly.

7. Hence, on the basis of the established distinction between the different conditions of Crohn's disease and starting from Dr Wolman's disclosure in document (9) as representing the closest state of the art, the problem the patent in suit sets out to solve was that of providing further uses for the medicament budesonide in addition to those already disclosed in the state of the art. The solution to the problem comprises the use of budesonide, or the 22 epimer thereof, in the preparation of a pharmaceutical composition for the treatment of the various conditions of Crohn's disease specified in claims 1 to 3 of the appellant's current requests.

7.1 The patent in suit claims that the specific conditions of Crohn's disease set out in claims 1 to 3 can successfully be treated by the administration of orally delivered budesonide to patients in need of it. In his written submissions and during the oral proceedings, the respondent suggested that, in the absence of clinical trials and clinical data in the contested patent, it was doubtful whether the use of budesonide covered by present claims 1 to 3 would in each and every case enable a successful treatment of the different kinds of Crohn's conditions, but did not substantiate this with any evidence. However, a mere doubt on the part of the respondent cannot prevent the effects and capabilities ascribed to the claimed uses

of budesonide in the patent in suit being taken into account when formulating the problem (see eg T 219/83, OJ EPO 1986, 211).

7.2 On the basis of the disclosure of the claimed invention in the patent in suit, the state of the art, which generally teaches the usefulness of glucocorticosteroid compounds in the treatment of Crohn's disease and the specific use of budesonide in the treatment of Crohn's disease reported in (9), the board sees, *prima facie*, no reason to doubt that the problem in its different aspects has been solved.

8. In citation (9) itself, Dr Wolman makes **no explicit claim** to have effected relapse prevention treatment. The conclusion in the impugned decision that the disclosure of (9) takes away the novelty of the use of budesonide for relapse prevention in the small intestine goes, in the board's judgment, beyond what is directly and ambiguously derivable from the teaching of the cited document. The opposition division's conclusion was essentially based on the observation in (9) that reduction of the dosage regimen from 10 caps/day to 8 caps/day resulted in recurrent pain but resolved on returning to 10 caps/day.

8.1 On the basis of the explanations given in the declarations of Professor Rutgeerts (see eg paragraphs 8-10) and Professor Hermon-Taylor (see eg paragraphs 15, 16), including the pieces of prior art cited therein, one cannot exclude that recurrence of pain reported in (9) may in fact have been due to a dosage regimen too low to achieve effective remission of Crohn's disease. Moreover, the state of the art cited in the above-mentioned declarations (see eg

Summers et al; Gastroenterology 1979, Vol. 77, 847-870) would appear to suggest that in citation (9) the patient's condition was not monitored long enough for a clear conclusion to be drawn to the effect that relapse prevention had indeed occurred.

In the board's judgment, citation (9) does not disclose clearly and unequivocally the treatment of Crohn's disease in the small intestine as relapse preventing treatment and does not, accordingly, destroy the novelty of claim 1 of all the requests.

8.2 The patient in (9) was diagnosed pre- and postoperatively as suffering from "terminal ileal Crohn's disease". Since the treatment of conditions of Crohn's disease in the colon is neither explicitly nor implicitly disclosed in the Wolman paper, (9) cannot destroy the novelty of claims 2 and 3 either which relate to Crohn's colitis in its active phase and Crohn's colitis in its chronic phase as relapse preventing therapy.

8.3 The proposed solution to the stated problem according to all three requests is therefore deemed to be novel within the meaning of Article 54(1) EPC.

9. The only issue remaining is therefore whether the proposed solution involves an inventive step.

Main request

9.1 Claim 2 relates to the use of budesonide or the 22R epimer thereof in the preparation of a pharmaceutical composition for the treatment by the oral route of Crohn's colitis in its active phase. Citation (9)

provides treatment of active Crohn's disease of the terminal ileum.

9.2 The person skilled in the art, should he really need this information, could see from Figure 1 on page 1812 of (1) that the terminal ileum is directly connected to the colon. Document (1) discloses that the glucocorticosteroid compound prednisolone is effective in the treatment of terminal ileal Crohn's disease, Crohn's ileocolitis in its active phase, ie a condition where the disease occurs simultaneously in the ileum and the colon, and is likewise effective in combination with salazosulfapyridine in the treatment of Crohn's colitis (see 1814, right-hand column, last three paragraphs).

Citation (4) suggests that orally delivered 6-methyl prednisolone is effective for all disease locations, in particular for the treatment of Crohn's conditions of the ileum or the colon (see page 29, lines 15 to 17, from the bottom.

9.3 In the board's view, the skilled person faced with the stated technical problem would have been aware from his knowledge in anatomy of the direct connection of the terminal ileum and colon in the gastrointestinal tract. From his knowledge of the prior art he would also have been aware of the successful treatment of Crohn's conditions of the terminal ileum on the one hand, and the colon on the other by the oral administration of one and the same glucocorticosteroid compound. On the basis of this knowledge the person skilled in the art would have reasonably expected that orally delivered budesonide, which has been shown in (9) to be effective in the treatment of Crohn's disease in its active phase

in the terminal ileum, would be similarly effective in the treatment of Crohn's disease in its active phase in the following section of the bowel, ie the colon. In the present situation, this notional skilled person was provided with a clear hint from the prior art pointing him in the direction of the claimed use of budesonide, and it was only necessary to confirm experimentally that the highly probable result was in fact obtained. The necessity of experimentally confirming a reasonably expected result does not render an invention unobvious.

9.4 In view of what has been said above, the board finds that the use of budesonide according to claim 2 does not involve an inventive step contrary to the requirements of Article 52(1) in conjunction with Article 56 EPC.

Since a decision can only be taken on each request as a whole, there is no need to look into the patentability of the other claims.

First auxiliary request

9.5 At the priority date of the patent in suit, it was already known to a person skilled in the art that budesonide exhibits a topical local action rather than a systemic action. For example, (4) discloses on page 30 under the heading "Steroid Absorption" (see especially 2nd paragraph, lines 7 to 9): "The promising results with <.....> budesonide <.....> suggest that plasma concentrations are unimportant".

Further, (8) provides additional evidence of the predominantly local action of budesonide by stating: "Budesonide undergoes an extensive first-pass

metabolism to metabolites of minimal biologic activity, which accounts for the low frequency of systemic effects" (see page 988, left-hand column, lines 9 to 12).

The finding by Dr Wolman in (9) that treatment of his patient with a regimen of budesonide 5 mg/day "did not result in systemic side effects of steroids" (see page 147, lines 3 to 4) also clearly points the skilled person to the predominantly local action of budesonide.

9.6 For a person skilled in the art knowing that budesonide acts predominantly locally, it was obvious to use for the treatment of Crohn's colitis in its active phase a controlled release formulation which releases its budesonide content in sufficient concentration in that part of the bowel where the disease resides to exert its local topic action. Suitable formulation techniques to provide oral compositions of budesonide fulfilling all requirements of controlled release were, at the priority date, already well known to a person skilled in the art (see eg citation (12)).

9.7 In view of the foregoing, the board finds that the use of budesonide according to claim 2 of the first auxiliary request does not involve an inventive step and that this request is accordingly not patentable either.

Second auxiliary request

9.8 At the priority date of the patent in suit it was already known that it would be strongly desirable for the treatment of specific conditions of Crohn's disease, eg Crohn's colitis, to have preparations which

release a major part of its drug content in the lower part of the intestinal system, preferentially in the large intestine, ie colon (see (12), paragraph bridging pages 1 and 2). Citation (12) suggests solving this problem by the provision of a multiple unit composition in a capsule wherein the units which contain the respective active component or drug are enteric-coated. Suitable coatings mentioned in (12) are, for example, anionic carboxylic acrylic polymers soluble only above pH 5.5 (see (12), page 3, line 11 onwards).

9.9 The subject-matter of claim 2 of the second auxiliary request results from an obvious combination of the teachings of citations (9) and (12). It follows that the second auxiliary request is not acceptable either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Townend P. A. M. Lançon