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Datasheet for the decision of 12 June 2008

Case Number: T 1238/05 - 3.3.02

Application Number: 96905292.7

Publication Number: 0812195

IPC: A61K 31/445

Language of the proceedings: EN

Title of invention:
Pharmaceutical composition for piperidinoalkanol compounds

Patentee:
Aventis Pharmaceuticals Inc.

Opponents:
Hexal Pharmaforschung GmbH
STADA Arzneimittel AG

Headword:
Compositions of fexofenadine hydrochloride/AVENTIS PHARMACEUTICALS

Relevant legal provisions:
EPC Art. 123(2), 56

Relevant legal provisions (EPC 1973):
-

Keyword:
"Auxiliary requests 3-8, 10-12: admissibility (no), not clearly allowable"
"Main request; auxiliary requests 1, 2, 9: inventive step (no), obvious combination of prior art teachings"
"Auxiliary requests 13, 16: added matter (yes), undisclosed combination of features"

Decisions cited:
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Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1238/05 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 12 June 2008

Appellant: (Patent Proprietor)
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Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 28 July 2005 revoking European patent No. 0812195 pursuant to Article 102(1) EPC 1973.

Composition of the Board:

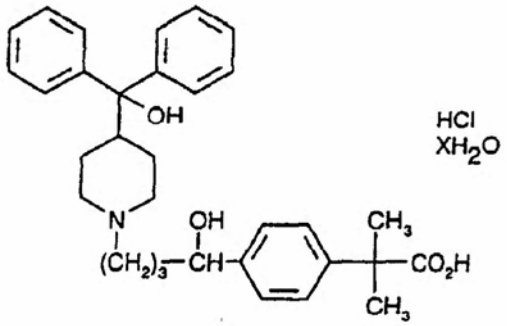
Chairman: U. Oswald
Members: M. C. Ortega Plaza
J. Van Moer

Summary of Facts and Submissions

I. European patent No. 0 812 195, which was filed as application number 96 905 292.7, based on international application WO 96/26726, was granted on the basis of twenty-two claims of product category, thirteen of which were independent. Independent claims 8 and 11, and dependent claim 12 as granted read as follows:

8. A pharmaceutical composition in solid unit dosage form, comprising;

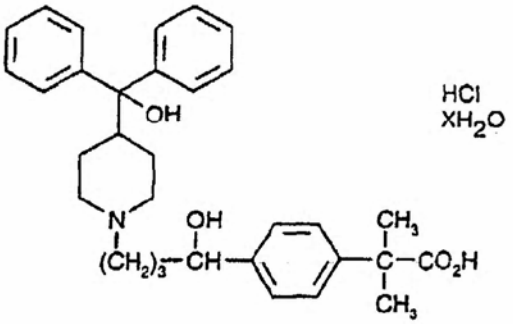
a) a therapeutically effective amount of a piperidinoalkanol compound of the formula;



wherein X is a number ranging from about zero to 5, and the individual optical isomers thereof; and
b) inert ingredients comprising microcrystalline cellulose, pregelatinized starch, magnesium stearate, calcium carbonate and sodium starch glycolate in amounts of about 20% to about 85%, 5% to about 50%, 0.05% to about 3%, 5% to about 50% and 1% to about 15%, respectively, by weight of the composition.

11. A pharmaceutical composition in solid unit dosage form, comprising;

a) a therapeutically effective amount of a piperidinoalkanol compound or a pharmaceutically acceptable salt thereof wherein said piperidinoalkanol compound is of the formula:



wherein X is a number ranging from about zero to 5, and the individual optical isomers thereof; and
b) croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, and magnesium stearate in amounts of about 1% to about 10%, 20% to about 85%, 5% to about 50% and 0.05% to about 3%, respectively, by weight of the composition.

12. The pharmaceutical composition in solid unit dosage form according to claim 11 wherein croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, and magnesium stearate are present in amounts of about 6%, 33.3%, 30% and 0.75%, respectively, by weight of the composition.

II. The following documents were cited *inter alia* during the proceedings:

(1) US 4 929 605
(2) US 4 254 129
(3) "Pharmaceutics: The Science of Dosage Form Design", 1988, M.E. Aulton (editor), chapter 18, 304-321
(5) Expert opinion by Prof. Dr. Henning Blume entitled "Gutachten zur Vergleichbarkeit der Bioverfügbarkeit verschiedener Fexofenadin-Zubereitungen", filed by the opponents with letter of 21 April 2005
(5a) BASF ExAct, July 1999, No. 2, pages 5 to 13

III. Oppositions were filed against the granted patent by opponents 1 and 2. The patent was opposed under Article 100(a) EPC for lack of novelty and inventive step.

IV. The appeal lies from the decision of the opposition division revoking the patent under Article 102(1) EPC (version 1973). The decision was based on the set of claims as granted.

The opposition division considered the subject-matter claimed to be novel since none of the cited documents disclosed the specific combination of features according to claims 8 to 10 and 11. These claims were

the only claims for which the opponents had contested novelty.

With respect to the issue of inventive step, the opposition division considered document (2) to represent the closest prior art and defined the problem to be solved as lying in the provision of oral pharmaceutical formulations of fexofenadine hydrochloride which show a higher bioavailability.

The opposition division considered that the proposed solution to said problem lacked and inventive step in view of document (1), which suggested the addition of inert ingredients such as those defined in claim 8 of the patent in suit as a solution to the above-mentioned problem.

Furthermore, the opposition division indicated that the result of its analysis would have been the same had it started with document (1) as closest prior art, in combination with the disclosure of document (2). In this context, the opposition division was of the opinion that the comparative tests filed by the patent proprietor with letter of 10 February 2004 did not convincingly demonstrate any advantageous properties of the compositions according to claim 8 with respect to those disclosed in document (1).

V. The appellant (patentee) lodged an appeal against this decision, and filed with the grounds of appeal additional data and documents, a main request and an auxiliary request.

VI. The respondents (opponents 1 and 2) filed counterarguments.

VII. In the communication accompanying the summons to oral proceedings, the board expressed its preliminary opinion and noted, *inter alia*, that each of the independent product claims as granted would require a separate analysis, and that, owing to the use of the term "comprising", the defined components were to be viewed as representing a non-exhaustive list of ingredients present in the claimed compositions.

VIII. With the letter of 11 April 2008, respondent opponent 2 announced that it would not be attending oral proceedings.

IX. With the letter of 9 May 2008, the appellant filed a main request and auxiliary requests 1 to 12 to replace all previously filed requests.

The newly filed **main request** differed from the claim set as granted in the deletion of claims 8 to 10, 18 and 21.

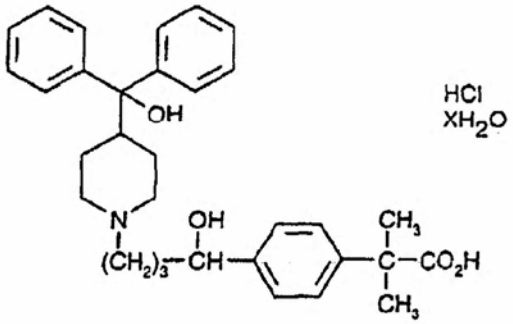
Auxiliary requests 1, 2 and 9 differed from the main request in the further deletion of claims.

The main request and auxiliary requests 1, 2 and 9 each included an independent claim identical to claim 11 as granted, as well as a dependent claim corresponding to claim 12 as granted, which are reproduced under point I above (cf. main request: claims 8 and 9; auxiliary requests 1, 2 and 9: claims 6 and 7, claims 3 and 4, and claims 1 and 2; respectively).

Auxiliary request 3 contained four independent claims directed to tablets (claims 1, 3, 5 and 8). Claim 8, which was derived from claim 11 as granted (cf. point I above), read as follows:

Tablet consisting of (i) a
8 ~~X~~. A pharmaceutical composition ~~in solid unit dosage form, comprising~~ consisting of

a) a therapeutically effective amount of a piperidinoalkanol compound or a pharmaceutically acceptable salt thereof wherein said piperidinoalkanol compound is of the formula:



wherein X is a number ranging from about zero to 5, and the individual optical isomers thereof; and
b) croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, and magnesium stearate in amounts of about 1% to about 10%, 20% to about 85%, 5% to about 50% and 0.05% to about 3%, respectively,

by weight of the composition, and optionally (ii) a coating.

In addition, auxiliary request 3 contained one independent claim directed to hard gelatin capsules (claim 12), which read as follows:

"Hard gelatin capsule filled with a pharmaceutical composition as defined in any one of claims 1 to 11".

Auxiliary requests 4 to 8, 10 and 11 differed from auxiliary request 3 in the deletion of claims and/or the restriction of certain claims to tablets and others to hard gelatin capsules. Each of these requests included a claim identical to claim 8 of auxiliary

request 3 (cf. claims 6, 3, 8, 6, 3, 1 and 1 of auxiliary requests 4 to 8, 10 and 11, respectively).

Auxiliary request 12 also contained an independent claim 2 corresponding to claim 8 of auxiliary request 3 wherein the ranges defining the amounts of excipients had been restricted according to claim 12 as granted (cf. point I above).

X. With the letter of 2 June 2008, respondent opponent 1 confirmed that it would also not be attending oral proceedings. Both respondents confirmed their request for revocation of the patent in its entirety.

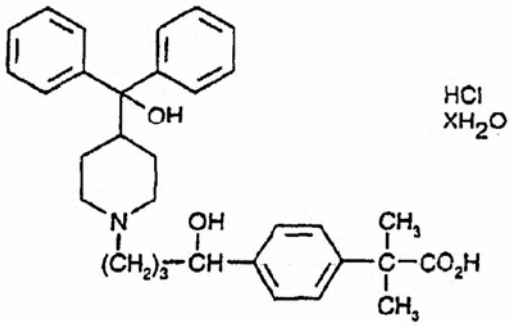
XI. Oral proceedings were held before the board on 12 June 2008.

Following the discussion on the admissibility of the requests filed with the letter of 9 May 2008, the appellant filed two sets of claims designated as auxiliary requests 13 and 16.

Auxiliary request 13 mainly differed from auxiliary request 3 in the amendment of the first line of each of the independent claims 1, 3, 5 and 8 to read "a pharmaceutical composition consisting of…" and in that, in the last line of each of said claims, "…and optionally (ii) a coating" had been replaced by "…wherein the pharmaceutical composition is in the form of an optionally coated tablet". Thus, claim 8 of auxiliary request 13 read as follows:

8 A pharmaceutical composition ~~in solid unit dosage form, comprising~~ consisting of

a) a therapeutically effective amount of a piperidinoalkanol compound or a pharmaceutically acceptable salt thereof wherein said piperidinoalkanol compound is of the formula:



wherein X is a number ranging from about zero to 5, and the individual optical isomers thereof; and
b) croscarmellose sodium, microcrystalline cellulose, pregelatinized starch, and magnesium stearate in amounts of about 1% to about 10%, 20% to about 85%, 5% to about 50% and 0.05% to about 3%, respectively,

by weight of the composition, [-]

[wherein the pharmaceutical composition is in the form of an optionally coated tablet.]

In addition, claim 12 of auxiliary request 13 differed from claim 12 of auxiliary request 3 in that it referred to "Hard or soft gelatin capsule".

Auxiliary request 16 differed from auxiliary request 13 mainly in the deletion of claim 12 and the amendment of independent claim 1 and dependent claim 2 to relate to a "hard or soft gelatin capsule".

XII. The appellant's arguments, in so far as they are relevant to the present decision, can be summarized as follows:

With respect to the issue of admissibility of the requests filed with the letter of 9 May 2008, the appellant submitted that these requests had been filed as a direct response to the preliminary opinion expressed by the board in the communication accompanying the summons to oral proceedings.

In particular, the appellant argued that the wording adopted in auxiliary requests 3 to 8 and 10 to 12 filed with the letter of 9 May 2008 was a response to the comment in said communication that "the defined components are to be viewed as representing a non-exhaustive list of ingredients present in the claimed compositions". The appellant submitted that, with the amendments introduced, the subject-matter claimed had been restricted to particular solid unit dosage forms, namely, tablets, coated tablets and hard gelatin capsules as disclosed on page 15, lines 4 to 6 of the application as originally filed, and that the list of ingredients therein was now clearly to be considered as being exhaustive.

As regards the admissibility of auxiliary requests 13 and 16 filed during the oral proceedings, the appellant argued that they were based on previously filed auxiliary requests 3 and 6, amended to take into account concerns relating to admissibility raised by the board at oral proceedings.

With respect to the basis in the application as originally filed for auxiliary requests 13 and 16 (Article 123(2) EPC), the appellant pointed to the fact that claim 3 as originally filed specified that the claimed pharmaceutical compositions were in solid unit dosage form, and that the specific examples of solid unit dosage forms listed on page 15, lines 4 to 8 included tablets, coated tablets, and hard or soft gelatin capsules, whereby capsules and tablets were preferred.

The appellant further referred to the passage in the description on page 26, line 17 to page 28, line 6 as disclosing the specific combination of inert ingredients now claimed, and argued that, particularly in view of the reference to capsules and tablets on page 28, line 5, this passage would clearly be read within the context of the disclosure of solid unit dosage forms disclosed on page 15, lines 4 to 8.

With respect to claim 8 of auxiliary requests 13 and 16, the appellant submitted that additional support could be found on page 29, lines 19 to 35, and in example 14 of the application as originally filed.

Concerning the issue of inventive step of the main request and auxiliary requests 1, 2 and 9 filed with the letter of 9 May 2008, the appellant's submissions in relation to the independent claim that was common to all these requests, namely, claim 8 of the main request, and claims 6, 3 and 1 of auxiliary requests 1, 2 and 9, respectively, were as follows:

The appellant started from document (2) as closest prior art, although it noted that this document specifically disclosed pharmaceutical formulations in solid unit dosage form, but not containing fexofenadine as active ingredient (examples 9 and 10), as well as an aerosol formulation (in the form of a suspension) comprising fexofenadine but as a free base (example 12).

The appellant defined the problem to be solved as lying in the provision of alternative pharmaceutical formulations of fexofenadine.

According to the appellant, this problem had been solved by providing a solid unit dosage form comprising fexofenadine as hydrochloride in combination with specific inert ingredients, such as that defined in claim 8 of the main request. In this context, the appellant referred to data provided during the opposition procedure with the letter of 10 February 2004, and the further data submitted with the statement of grounds of appeal, as demonstrating that solid unit dosage forms according to the invention had good bioavailability, which was similar to that observed for formulations according to the prior art.

The appellant maintained that the proposed solution was not rendered obvious by the prior art.

The appellant argued that document (2) itself only disclosed fexofenadine in its free base form and did not give any clear hint to use the hydrochloride thereof (as hydrated or anhydrous form).

Furthermore, the appellant submitted that the only specific example in document (2) of a pharmaceutical formulation comprising fexofenadine related to an aerosol suspension rather than a solid unit dosage form (example 12), and that in the two examples disclosing solid unit dosage forms, i.e. examples 9 and 10, the active ingredient was completely different to fexofenadine.

In addition, the appellant maintained that the combinations of inert ingredients disclosed in examples 9 and 10 of document (2) were also different to that defined in claim 8 of the main request.

Thus, starting from example 9 or 10 of document (2), the appellant submitted that several modifications were required to arrive at the subject-matter now claimed, which would not have been obvious to the skilled person in view of the very general nature of the disclosure of solid unit dosage forms in document (2) (see column 5, lines 31 to 44)

Turning to document (1), the appellant argued that fexofenadine was not even disclosed as such and that no clear teaching could be derived from document (1) to modify the compositions according to document (2) in order to arrive at the claimed subject-matter.

In this context the appellant argued that every specific drug behaved differently and that the skilled person would not expect suitable compositions to be achieved by simply exchanging the active and inert ingredients in specific known compositions.

With reference to the solid unit dosage formulations exemplified in document (1) (Examples 1 and 2), the appellant further submitted that, according to document (1), it was essential to combine a nonionic surfactant with a carbonate salt (cf. claim 1), whereas such a surfactant was not necessary in the patent in suit.

In addition, the appellant emphasized that there was no teaching in documents (1) or (2) to use the disintegrant croscarmellose sodium, which was a mandatory excipient in claim 8 of the main request.

The appellant acknowledged that croscarmellose sodium was listed under the trade name Nymcel® in Table 18.4 of the textbook document (3) (page 314). However, the appellant maintained that it was to be found in a long list of possible tablet disintegrants, without any recognisable pointer to croscarmellose sodium as being preferred.

As evidence that not all disintegrants were inter-changeable, the appellant referred to document (5a), and specifically to the passage at the bottom right-hand corner of page 10 stating: "Gordon et al. 1993 investigated the influence of three so called "super disintegrants" on the dissolution of naproxen from granulated tablets on storage under different conditions and found that crospovidone and sodium starch glycolate were superior compared to croscarmellose sodium".

The appellant argued that, in view of this teaching, the skilled person would be even more unlikely to select croscarmellose sodium from the disintegrants listed in Table 18.4 of document (3).

The appellant acknowledged that each of the inert ingredients defined in claim 8 of the main request was known as such at the priority date of the patent in suit. However, the appellant argued that the key issue was not whether the skilled person could have theoretically chosen the hydrochloride salt of fexofenadine and combined it in solid unit dosage form with the specific inert ingredients as claimed, but whether the skilled person would have done so with a reasonable expectation of success. The appellant

submitted that, in the absence of any recognisable pointer in the prior art to the specific compositions claimed, this question had to be answered in the negative.

XIII. The respondents' arguments submitted in writing may be summarized as follows:

In their response to the statement of grounds of appeal, the respondents argued that the claimed subject-matter did not involve an inventive step.

In particular, the respondents challenged the validity of the comparative data submitted by the appellant during the opposition and appeal procedures. Furthermore, the respondents submitted that it was unclear what the appellant meant in asserting "good bioavailability" for the claimed formulations, and referred to the normalized data provided in the expert opinion document (5) as demonstrating that certain formulations according to the patent in suit yielded worse results than those of the comparative examples.

The respondents also pointed to the fact that the excipients as defined in the claims were all well-known in the art, and argued that it was a routine matter for the skilled person to substitute particular excipients in known tablet formulations for alternative excipients of identical function.

With reference to document (3), the respondents maintained that, for example, it would be an obvious measure for the skilled person to substitute the excipient starch glycolate sodium employed in the

formulations disclosed in document (1) for croscarmellose sodium, since both compounds had been known to act as disintegrants for solid unit dosage forms well before the priority date of the patent in suit.

XIV. The appellant (patentee) requested that the decision under appeal be set aside and the patent be maintained on the basis of the main request or any of the auxiliary requests 1 to 12, filed with letter of 9 May 2008 or 13th or 16th auxiliary requests, filed during the oral proceedings.

The respondents (opponents) requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Admissibility of late-filed requests*

2.1 The admissibility of late-filed requests is at the board's discretion and depends upon the overall circumstances of the case under consideration, account being taken *inter alia* of whether they could have been filed earlier and if so the reason why they were not, and of whether they fulfil the criterion of clear allowability.

2.2 The main request and auxiliary requests 1, 2 and 9 filed with the letter of 9 May 2008 are admissible since they only differ from the claim set as granted in

the deletion of claims, with consequent renumbering of claims and adjustment of dependencies. These simple restrictions are a clear and direct response to the communication sent as an annex to the invitation to oral proceedings.

2.3 Auxiliary requests 3 to 8 and 10 to 12 filed with the letter of 9 May 2008 all contain claims directed to a "tablet consisting of (i) a pharmaceutical composition consisting of …, and optionally (ii) a coating" (cf. point IX above).

The appellant stated that these claims were intended to cover two solid unit dosage forms, namely, "tablets" and "coated tablets", both disclosed in the application as originally filed.

However, the feature "and optionally (ii) a coating" does not necessarily imply that the tablet itself is coated. The claims' wording also encompasses the possibility that an inner core or granules within the tablet may be coated, which is common in controlled-release formulations. No basis can be found in the application as originally filed for solid dosage forms of this type.

Hence, the amendments introduced raise, *prima facie*, new issues of added matter (Article 123(2) EPC) and/or lack of clarity (Article 84 EPC) at a very late stage in the procedure.

Accordingly, auxiliary requests 3 to 8 and 10 to 12 are not admitted into the proceedings.

2.4 In auxiliary requests 13 and 16 filed during oral proceedings, the wording objected to at the oral proceedings for auxiliary requests 3 to 8 and 10 to 12 was replaced by "a pharmaceutical composition consisting of … wherein the pharmaceutical composition is in the form of an optionally coated tablet". This amendment is a clear and direct response that successfully overcomes the objections regarding admissibility based on the requirement that late-filed claims should be *prima facie* allowable. Therefore, these requests are admitted into the proceedings.

3. *Main request and auxiliary requests 1, 2 and 9*

3.1 *Amendments*

Article 100(c) was not given as a ground for opposition in the present case. Moreover, since the main request and auxiliary requests 1, 2 and 9 only differ from the claim set as granted in the deletion of claims, there can be no question of objections to these amendments under Articles 84, 123(2) or 123(3) EPC.

3.2 *Novelty (Articles 52(1) and 54 EPC)*

The board is satisfied that the claimed subject-matter is novel over the cited prior art.

In the contested decision, the opposition division acknowledged the novelty of the subject-matter claimed. Moreover, claims 8 to 10 as granted, objected to as lacking novelty during opposition proceedings, have been deleted, and the novelty of the remaining claims

has not been contested in appeal proceedings. Hence, no detailed reasoning in this respect is required.

3.3 *Inventive step (Articles 52(1) and 56 EPC)*
Main request - independent claim 8

The subject-matter of claim 8 relates to a pharmaceutical composition in solid unit dosage form, comprising fexofenadine hydrochloride (with about 0 to 5 water molecules) and four specific excipients in defined ranges of amounts.

Document (2) represents the closest prior art. This has not been disputed by the appellant.

Document (2) relates to piperidinoalkanol derivatives of Formula I and pharmaceutically acceptable salts thereof, their use as antihistamines, antiallergy agents and bronchodilators, and pharmaceutical formulations thereof (see column 1, lines 5 to 58 and claims 1, 10 and 11). In particular, claim 8 discloses fexofenadine (4-[4-[-4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-hydroxybutyl]-α,α-dimethylbenzeneacetic acid) or a pharmaceutically acceptable salt thereof.

Document (2) further discloses pharmaceutical compositions "in solid or liquid form such as, tablets, capsules, powders, solutions, suspensions or emulsions" (column 5, lines 1 to 7). In particular, document (2) states in column 5, lines 31 to 44 (emphasis added):

"The solid unit dosage forms can be of the conventional type. Thus, the solid form can be a capsule which can be the ordinary gelatin type containing a novel

compound of this invention and a carrier, for example, lubricants and inert fillers such as lactose, sucrose or cornstarch. In another embodiment the novel compounds are **tableted with conventional tablet bases** such as lactose, sucrose or cornstarch **in combination with binders** such as acacia, cornstarch or gelatin, **disintegrating agents** such as cornstarch, potato starch or alginic acid, **and a lubricant** such as stearic acid or magnesium stearate".

Although document (2) does not illustrate specifically a pharmaceutical formulation comprising fexofenadine hydrochloride, it specifically discloses a tablet comprising fexofenadine as its ethyl ester, starch, lactose and magnesium stearate (example 10).

Hence, in the light of the closest prior art, the problem to be solved lies in the provision of further pharmaceutical formulations of fexofenadine.

The solution as defined in claim 8 relates to a formulation of fexofenadine in the form of its hydrochloride salt together with the mandatory excipients croscarmellose sodium, microcrystalline cellulose, pregelatinized starch and magnesium stearate.

The board is satisfied that the problem has been plausibly solved in the light of the description and the examples of the patent in suit, in particular example 14, confirmed by the additional test results in Table 2 filed during opposition proceedings with the letter of 10 February 2004 (see in particular page 8, example F).

It remains to be investigated whether the proposed solution is obvious to the skilled person in the light of the prior art.

Document (2) clearly discloses fexofenadine as a preferred active ingredient. Indeed, fexofenadine was the compound chosen to demonstrate the utility of the claimed compounds of generic formula I (see column 6, lines 7 to 14). In addition, claim 8 specifically relates to fexofenadine or a pharmaceutically acceptable salt thereof, and claim 7 to its ethyl ester or a pharmaceutically acceptable salt thereof.

Moreover, document (2) discloses hydrochloric acid at the top of the list of suitable inorganic acids for the formation of acid addition salts (column 3, line 32).

Accordingly, starting from example 10 of document (2), it would have been an obvious measure for the skilled person, faced with the above-mentioned problem, to substitute the ethyl ester of fexofenadine for fexofenadine hydrochloride.

Furthermore, as already mentioned, document (2) teaches tableting with conventional tablet bases in combination with binders, disintegrating agents and lubricants.

The skilled person seeking further combinations of inert ingredients as taught in document (2) is aware of the conventional excipients for the formulation of solid unit dosage forms available at the priority date of the patent in suit, such as those listed in documents (1) and (3).

Thus, document (1), which concerns the provision of pharmaceutical compositions in solid unit dosage form (see column 3, lines 10 to 15) for oral administration of, *inter alia*, the piperidinoalkanol derivatives disclosed in document (2) (see column 1, lines 13 to 16 and 37 to 42), lists a number of "therapeutically inert ingredients such as are well known and appreciated in the art of pharmaceutical science", including binders such as pregelatinized starch, conventional carriers and fillers such as microcrystalline cellulose, and lubricants such as magnesium stearate (see column 4, lines 10 to 26).

Similarly document (3), which is a standard textbook covering the design of dosage forms and relates in its chapter 18 to "Tablets", refers to microcrystalline cellulose as a "very popular diluent" and magnesium stearate as "the most popular lubricant" (see page 310, left-hand column, line 7 and page 311, right-hand column, second complete paragraph). Furthermore croscarmellose sodium is listed as a tablet disintegrant under the trade name Nymcel® in Table 18.4 (page 314).

Thus, the excipients listed in claim 8 of the main request are all commonly used excipients in the field of pharmaceutical technology. This is confirmed in the patent in suit (see paragraph [0054]): "As used herein the term "inert ingredient" refers to those therapeutically inert ingredients that are well known in the art of pharmaceutical science which can be used singly or in various combinations …"

Therefore, the combination of excipients as claimed in claim 8 of the main request must be regarded as a straightforward choice which the skilled person would select without the exercise of inventive skill.

Concerning the respective amounts of excipients appearing in claim 8, the broad ranges defined encompass the usual amounts foreseen in the prior art formulations and generally known to the skilled person (cf. e.g. document (1), column 4, lines 32 to 40 and document (3), tables 18.3 and 18.4). Therefore, this feature also cannot not serve as a basis for the acknowledgment of an inventive step.

In view of the above analysis, the solution proposed in claim 8 of the main request is obvious in the light of prior art.

Under these circumstances, there is no need to consider the remaining claims of the main request.

3.4 The appellant's arguments in favour of an inventive step for claim 8 of the main request do not hold for the following reasons:

3.4.1 It cannot be accepted that the claimed subject-matter plausibly solves the problem of providing alternative pharmaceutical compositions of fexofenadine, i.e. compositions having comparable bioavailability to compositions according to the prior art.

The appellant has submitted a series of tests in which the bioavailability for various compositions in solid unit dosage form according to the patent in suit were

compared with that of a composition based on example 1 of document (1), which contained the inert ingredients employed in said example, in similar percentages by weight, but wherein the active ingredient was substituted for fexofenadine hydrochloride (see letter of 10 February 2004 filed during opposition procedure, point 5.3, particularly Tables 1, 2 and 4, and Table 5, comparative example 2; and statement of grounds of appeal, points 3.3.2.2 and 3.3.2.3).

However, the data provided do not allow a fair comparison since the entries not only differ in the nature of the inert ingredients present in the pharmaceutical compositions, but additionally in other essential characteristics such as the administered amount of fexofenadine hydrochloride, the nature of the solid unit dosage form (i.e. capsules or tablets) and/or the number of units administered in a single dose. Moreover, these additional differences, which are all factors expected to influence the results obtained, are not reflected by the features defined in claim 8 of the main request.

In particular, attention is drawn in this context to Table 2 submitted with the letter of 10 February 2004 (page 8). Example F of Table 2 pertains to a composition according to claim 8 (cf. letter of 10 February 2004, Table 1). In example F, the amount of fexofenadine hydrochloride administered is **180 mg** in the form of a **single tablet**, whereas in the comparative example using the formulation according to document (1) a dose of **90 mg** is administered as **three 30 mg tablets** (cf. letter of 10 February 2004, Table 5, comparative example 2). This cannot be regarded as a valid

comparison, owing to the differences in the administered dose and in the number of tablets administered, since both parameters are expected to influence the results obtained. This can also be inferred from said Table 2, namely, from the different results obtained in examples H and I and in examples A and H, respectively. Moreover, several other divergences precluding a straight comparison may be noted, such as the differences in percentage by weight of fexofenadine hydrochloride with respect to inert ingredients.

Accordingly, in the absence of a proper comparison, no conclusion can be drawn as to the relative merits of the formulations as claimed compared with those according to the prior art.

3.4.2 The argument that there is a lack of clear incentive in document (2) to use fexofenadine hydrochloride as active ingredient is also not convincing.

As was explained under point 3.3 above, there is a clear teaching in document (2) of pharmaceutically acceptable salts of fexofenadine, such as the hydrochloride, as the suitable active ingredient. Moreover, both fexofenadine hydrochloride and fexofenadine ethyl ester share the same active principle, namely, fexofenadine, which is derivatized either as hydrochloride salt or hydrolysable ester.

3.4.3 In addition, it cannot be accepted that the skilled person, in view of the teachings of document (1) and (3), would not have chosen to combine the hydrochloride salt of fexofenadine in solid unit dosage form with the

specific inert ingredients as claimed with a reasonable expectation of success.

What the skilled person would be motivated to do depends on the problem that it wishes to solve. In the present case the problem to be solved is to provide further pharmaceutical formulations of fexofenadine.

As explained above, the claimed inert ingredients are disclosed in documents (1) and (3) as commonly used excipients for use in solid unit dosage forms. Hence, the skilled person would certainly have considered them as suitable candidates when seeking further tablet bases, binders, disintegrating agents and lubricants. Thus, textbook document (3) lists in Table 18.4 twelve tablet disintegrants, which would be regarded by the skilled person as equally suitable options. In view of the problem to be solved as defined above, the skilled person would not be deterred by the fact that there is no pointer to croscarmellose sodium as being preferred.

It is true that document (1) particularly claims pharmaceutical compositions in which a nonionic surfactant and a carbonate salt are mandatory components (see claim 1), but these are offered as a solution to the more specific problem of providing a composition "which allows efficient and immediate absorption and bioavailability" (cf. column 1, lines 30 to 33). However, the general teaching of document (1) remains relevant in the context of providing suitable excipients for pharmaceutical formulations of fexofenadine. Moreover, since the problem to be solved only relates to the provision of further formulations, the skilled person would not be deterred by the

specific teaching of document (1) from using in further formulations the additional conventional inert ingredients disclosed in document (1). In addition, it is noted that, owing to the use of the term "comprising", claim 8 of the main request does not exclude the presence of a nonionic surfactant or a carbonate salt, as disclosed in document (1).

Similarly, no deterrent teaching with respect to the use of croscarmellose sodium can be derived from the post-published document (5a). The passage referred to by the appellant refers to a quotation from an earlier document about a comparative study on the dissolution of naproxen from granulated tablets with various disintegrants. Given that naproxen has a completely different chemical and physical structure to fexofenadine, the alleged superior results for crospovidone and sodium starch glycolate would not lead the skilled person to conclude that croscarmellose sodium is an unsuitable disintegrant for tableting fexofenadine hydrochloride.

3.5 Accordingly, the main request is rejected for lack of inventive step (Article 56 EPC).

3.6 *Inventive step (Articles 52(1) and 56 EPC)*
Auxiliary requests 1, 2 and 9

Auxiliary requests 1, 2 and 9 each contain a claim identical to that of claim 8 of the main request (see claims 6, 3 and 1, respectively).

Consequently, auxiliary requests 1, 2 and 9 are also rejected for lack of inventive step (Article 56 EPC).

4. *Auxiliary requests 13 and 16 - claim 8*
Article 123(2) EPC

4.1 Auxiliary requests 13 and 16 each contain an identical claim 8, which is reproduced above under point XI.

Said claim 8 originates from independent claim 3 in combination with claims 5, 7, 22 and 23 as originally filed. In particular, fexofenadine hydrochloride (with about 0 to 5 water molecules) is specified in claim 5, and the four specific excipients together with the ranges of amounts now claimed are disclosed in claim 23 as originally filed.

However, several additional specifications have taken place, namely, by means of the replacement of "comprising" with "consisting of", and in view of the fact that the pharmaceutical composition is now "in the form of an optionally coated tablet".

The question therefore arises whether the combination of the specific solid unit dosage form "(optionally coated) tablet" with the specific pharmaceutical composition as defined in claim 8 can be directly and unambiguously derived from the application as originally filed.

4.1.1 In the claim set as originally filed, there are several references to tablets, namely, in claims 34, 37, 40, 42 and 43. However, this cannot be taken as a basis for claim 8 of auxiliary requests 13 and 16, *inter alia* because none of said claims relate to a composition as defined in claim 23 as originally filed. Moreover, none

of the claims refer to a tablet that may be optionally coated.

4.1.2 Turning to the description as originally filed, the first paragraph of the "summary of the invention" states (see page 2, lines 10 to 15):

"The present invention provides a pharmaceutical composition in solid unit dosage form, comprising,
a) a therapeutically effective amount of a piperidinoalkanol compound or a pharmaceutically acceptable salt thereof; and
b) at least one inert ingredient."

This disclosure corresponds to independent claim 3 as originally filed.

Thus, the generic pharmaceutical composition is defined in a very broad manner, without singularizing either the active ingredient, or the number and nature of inert ingredients.

A generic disclosure of the piperidinoalkanol compound, the solid unit dosage forms and the inert ingredients envisaged can be found on pages 3 to 7, 15, and 25 to 27 of the description as originally filed.

Thus, the term "piperidinoalkanol compound or a pharmaceutically acceptable salt thereof" is further defined in terms of three generic Markush formulae (I) to (III) (pages 3 to 5). Preferred, compounds falling within the scope of formula (III) are disclosed on pages 6 and 7 as formulae (IIIa) and (IIIb), whereby formula (IIIa) represents fexofenadine hydrochloride

and its hydrates, i.e. the formula of claim 8 of auxiliary requests 13 and 16, and formula (IIIb) fexofenadine free base and its hydrates.

On page 15, lines 2 to 9, it is generally disclosed that (emphasis added): "The pharmaceutical composition of the present invention is administered orally in the form of a solid unit dosage form. Examples of solid unit dosage forms are **tablets**, **coated tablets**, powders, dragees, hard or soft gelatin capsules and the like. The preferred solid unit dosage forms of the present invention are capsules, tablets and the like. The most preferred solid unit dosage form are tablets."

As regards the generic disclosure of suitable inert ingredients, suitable combinations of inert ingredients and amounts thereof, they are disclosed on page 25, line 20 to page 27, line 5, including the combination as defined in claim 8 of auxiliary requests 13 and 16 (see page 26, lines 27 to 32).

However, in order to arrive at the combination now claimed, particular features have to be selected from three different parts of the application, namely, the piperidinoalkanol compound of formula (IIIa) disclosed on page 6, a particular solid unit dosage form amongst those disclosed on page 15, lines 2 to 9 (i.e. tablet, coated or not), and the specific mixture of inert ingredients disclosed on page 26, lines 27 to 32.

Accordingly, the subject-matter of claim 8 of auxiliary requests 13 and 16 amounts to an unallowable selection from the generic disclosure outlined above, which

extends beyond the original content of the application (Article 123(2) EPC).

4.1.3 The embodiments disclosed in the remaining passages of the description as originally filed also cannot provide a basis for the subject-matter claimed:

Table 5 provides specific information about the "most preferred amounts of the respective inert ingredients which can be utilized in preparation of the **tablet or capsule dosage forms**" (page 27, lines 5 to 9, emphasis added). Entry #6 of Table 5 discloses a combination of excipients consisting of croscarmellose sodium, microcrystalline cellulose, pregelatinized starch and magnesium stearate in specific amounts expressed as specific percentages by weight of composition. Although these excipients correspond to the combination defined in claim 8 of auxiliary requests 13 and 16, their amounts given in Table 5 are very specific in contrast to the ranges appearing in claim 8 of auxiliary requests 13 and 16. Moreover, no preference is given to tablets, as opposed to capsules. In addition, a coated tablet is only mentioned for entries #2, #3, and #4, but not for entry #6 (cf. page 27, lines 33 to 35). Therefore, the claimed subject-matter is clearly not derivable from this section of the description as originally filed.

A further paragraph disclosing the combination of excipients as defined in claim 8 of auxiliary requests 13 and 16 can be found on page 29, lines 19 to 35. However, this paragraph discloses a particular process for producing tablets, with clear implications for the structural characteristics of the tablet obtained. In

addition, compounds of formula (IIIa) are not singled out as preferred active ingredients, the amounts of the various excipients are not specified, and only a film-coating is disclosed, rather than tablet coatings in general. Hence, this paragraph also cannot be accepted as a basis for the claimed subject-matter.

Similarly, the specific tablet disclosed in example 14 falls within the scope of claim 8 of auxiliary requests 13 and 16, but is clearly much more narrowly defined than the subject-matter claimed in the latter, for example with respect to the active ingredient, and the proportions and absolute amounts of ingredients present. Therefore, example 14 also cannot serve as a basis for claim 8, since this would constitute an unallowable generalisation of a specific embodiment.

4.1.4 Accordingly, it must be concluded that no direct and unambiguous basis can be found in the application as originally filed for the selection and combination of features now claimed in claim 8.

Under these circumstances, there is no need to consider the remaining claims of auxiliary requests 13 and 16.

4.2 The appellant's arguments in this respect cannot be accepted:

It must be emphasized that the sentence on page 15, lines 4 to 6, discloses "tablets, coated tablets" within a longer list of possible solid unit dosage forms. Thus, "optionally coated tablet" is not singled out as a preferred solid unit dosage form in the application as originally filed.

Moreover, this disclosure on page 15 must be read in the context of the very broad definition of the pharmaceutical composition as disclosed in the preceding passages of the description and in independent claims 1 and 3 as originally filed.

Finally, with respect to the passage on page 26, line 17 to page 28, line 6, referred to by the appellant it should be noted that no preference is specifically given therein to compounds of formula (IIIa), i.e. to fexofenadine hydrochloride in anhydrous or hydrated form, and certainly not in combination with tablets as opposed to capsules as preferred solid dosage form.

As explained under point 4.1 above, there is no direct and unambiguous disclosure in the application as originally filed that "tablets, coated tablets" as disclosed on page 15, lines 4 to 5, should be combined with formula (IIIa) and the specific inert ingredients in specific ranges of amounts as now claimed in claim 8.

4.3 In conclusion, auxiliary requests 13 and 16 have to be rejected since the subject-matter of claim 8 extends beyond the content of the application as originally filed (Article 123(2) EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald