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# D E C I S I O N
## of 26 October 2005

**Case Number:** T 1027/02 - 3.3.01

**Application Number:** 97830400.4

**Publication Number:** 0894794

**IPC:** C07D 295/08

**Language of the proceedings:** EN

**Title of invention:**
Optical isomers of cloperastine

**Applicant:**
AESCULAPIUS FARMACEUTCI S.r.l.

**Opponent:**
-

**Headword:**
Cloperastine/AESCULAPIUS FARMACEUTICI

**Relevant legal provisions:**
EPC Art. 123(2)

**Keyword:**
"Amendments: added subject-matter (yes)"

**Decisions cited:**
-

**Catchword:**
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 1027/02 - 3.3.01

# D E C I S I O N
**of the Technical Board of Appeal 3.3.01**
**of 26 October 2005**

**Appellant:** AESCULAPIUS FARMACEUTICI S.r.l.
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**Decision under appeal:** **Decision of the Examining Division of the European Patent Office posted 10 May 2002 refusing European application No. 97830400.4 pursuant to Article 97(1) EPC.**

**Composition of the Board:**

**Chairman:** A. Nuss
**Members:** P. P. Bracke
S. Perryman

## Summary of Facts and Submissions

I. The appeal lies from the Examining Division's decision refusing European patent application No. 97 830 400.4, since the then claimed pharmaceutical compositions were not novel over the disclosure of document

(3) EP-A-0 385 491.

II. At the oral proceedings before the Board of Appeal, which took place on 26 October 2005, the Appellant filed, as a main and sole request, a set of two claims, which read as follows:

"1. Process to prepare L(-) cloperastine hydrochloride, characterised by the following steps:

**Preparation of DL 4-chlorobenzhydryl-hemisuccinate**

dissolve DL 4-chlorobenzhydrol in ethyl acetate, stir vigorously, add 1.18 mols of succinic anhydride, 1.73 mols of triethylamine, and 0.073 mols of dimethylaminopyridine, all mols being expressed with respect to 1 mol of DL 4-chlorobenzhydrol. Then heat under reflux for a few hours until the reaction is complete.
Cool to room temperature and wash the solution obtained twice using de-ionized water.
Separate the phases, and treat the organic phase with a diluted solution of hydrochloric acid and then with de-ionized water. The organic phase is dehydrated and evaporated at reduced pressure until it is dry.
Purify the whitish residue thus obtained is [sic] by crystallization using toluene and n-heptane.

**Resolution of optical isomers of 4-chlorobenzhydryl with quinine**

dissolve DL 4-chlorobenzhydryl hemisuccinate in acetone, heat to 45-50 DEG C, stir vigorously, and add, in a time range of approximately 20 minutes, a hot solution made up of 1.13 mols of quinine (with respect to 1 mol of DL 4-chlorobenzhydryl hemisuccinate) dissolved in an acetone-methanol solution.
Under agitation, heat under reflux for 30 minutes and then cool the solution obtained to 0-5 DEG C.
Leave to rest at this temperature for a number of hours to favour complete precipitation of the product.

Separate by filtration the whitish precipitate thus obtained, consisting of D(+) 4-chlorobenzidryl-hemisuccinate of quinine is separated by filtration and sent on to the subsequent phases of recovery and/or synthesis of D(+) cloperastine.

Evaporate the solution obtained from filtration to dryness at a reduced pressure, and recover the whitish solid consisting of L(-) 4-chlorobenzidryl-hemisuccinate of quinine is obtained, which is sent on to the subsequent phase of hydrolysis.

**Hydrolysis and purification of 4-chlorobenzhydrol**

Dilute with methanol and 30% sodium hydroxide the solid residue obtained in the previous phase.

Heat at reflux under agitation for a number of hours and then evaporate the solvent at reduced pressure. The

residue obtained is treated with water and ethyl acetate, and the phases are separated.

The organic phase is washed again with water and then treated with 2N hydrochloric acid. The aqueous phase containing the optically active base is sent on for recovery of quinine.

Wash the ethyl acetate solution to neutral pH with de-ionized water and then dehydrate and evaporate until dry at reduced pressure.

Purify the low-melting solid thus obtained by crystallization using n-heptane, filtrate and dry

**Preparation of L(-) cloperastine hydrochloride**

Dissolve L(-) chlorobenzhydrol dissolved in methylene chloride and, stirring vigorously, add the chloro-ethyl-piperidine hydrochloride, tetrabutyl ammonium bisulphate and 30% sodium hydroxide.

Leave the mixture obtained under agitation for approximately 12 hours, maintaining the reaction temperature at 20-25 DEG C.

When the reaction is complete, add de-ionized water and separate the phases.

Wash the organic phase with 35% hydrochloric acid and then with de-ionized water.

Evaporate the methylene chloride at reduced pressure to obtain a low-melting solid, which is diluted with

methyl isobutyl ketone, and vacuum-dry again to remove even the last traces of methylene chloride.

Dilute the residue with fresh methyl isobutyl ketone, and then heat until a complete solution is obtained.

Cool to 0-5 DEG C for a few hours in order to favour complete precipitation of the product; then filter and vacuum-dry in an oven at 45-50 DEG C."

"2. Process to prepare L(-) cloperastine fendizoate, characterised by the following steps:

Dissolve in distilled water L(-) cloperastine hydrochloride as obtained in claim 1, add ethyl acetate and, stirring vigorously, bring up to a basic pH by adding 30% sodium hydroxide, maintaining the reaction temperature at 20-25 DEG C.

Separate the phases, and wash the organic phase with distilled water; then remove the solvent at reduced pressure.

Dissolve the oily residue in acetone and add, under vigorous stirring, to a hot solution of fendizoic acid in water and acetone.

Note the formation of a whitish precipitate, which is then cooled to room temperature and filtered and vacuum-dried in an oven at 55-60 DEG C."

III. The Appellant submitted that both claims according to the main request met the requirement of Article 123(2) EPC, since the steps in the claimed process

corresponded with those of phases a) to d) respectively of phase e) of example 1 in the application as filed and, thus, no subject-matter was added extending beyond the content of the application as filed.

IV. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request submitted at oral proceedings on 26 October 2005.

## Reasons for the Decision

1. The appeal is admissible.

2. *Article 123(2) EPC*

The relevant question to be decided in assessing whether subject-matter was added extending beyond the content of the application as filed, is whether the process features, in the claimed combination, were directly and unambiguously derivable from the application as filed.

2.1 The only information concerning processes for preparing L(-)cloperastine in the application as filed can be found in original Claim 5, on page 3, lines 3 to 19, and in example 1.

2.1.1 Original Claim 5 defines in general terms a process for preparing L(-)cloperastine fendizoate by resolution of the optical isomers of 4-chlorobenzhydrol with optically active bases, preparation of L(-)cloperastine HCl and salification with fendizoic acid.

Since the process in original Claim 5 is only defined in a very general manner, without defining any specific reaction circumstances, it is clear that the combination of all process features of present Claim 1 are not unambiguously derivable therefrom.

2.1.2 The passage on page 3, lines 3 to 19, of the application as filed only lists a number of advantageous effects obtained with the claimed process, such as its simplicity, reduced reaction time and excellent yield.

As this passage is completely silent about any specific reaction step, the combination of all process features of present Claim 1 are also not unambiguously derivable therefrom.

2.1.3 Thus, if existent, the only possible support for the processes of present Claims 1 and 2 could only be found in the passage describing phases a) to d) respectively phase e) of example 1 of the application as filed. This was not contested by the Appellant.

The phases a) to e) in example 1 of the application as filed describe the preparation of L(-)cloperastine hydrochloride or fendizoate starting from 120 g (0.55 mols) of DL 4-chlorobenzhydrol and adding specific amounts of the other reagents, and optionally converting 95 g L(-)cloperastine hydrochloride into the fendizoate. The Appellant agreed that the wording of present Claims 1 and 2 differ therefrom essentially in that the amount of starting DL 4-chlorobenzhydrol or L(-)cloperastine hydrochloride is not defined and that

the amounts of the other used reagents are defined as molar ratios based on DL 4-chlorobenzhydrol or L(-)cloperastine hydrochloride.

2.1.4 An amendment extends beyond the content of the application as filed if the amended subject-matter is not directly and unambiguously derivable from the content of the original application, even when taking into account matter which is implicit to a skilled person. In accordance with the well-established jurisprudence of the Boards of Appeal, this requirement clearly precludes allowing an amendment if there is any doubt as to whether or not it is derivable from the original application.

2.1.5 Consequently, the question arises, whether a skilled person reading the application as filed would have directly and unambiguously derived therefrom that the reaction circumstances described in phases a) to e) of example 1 for preparing L(-)cloperastine hydrochloride or fendizoate at laboratory scale would be applicable not only for the specific amounts described therein but also for any scale of production (pilot, semi-industrial, industrial), i.e. irrespective of the amounts to be produced, as long as the same molecular ratios are used.

Due to the small amounts of reagents used in example 1 of the application as filed, a skilled reader would immediately derive therefrom that phases a) to e) disclose experiments on a laboratory scale, a fact which the Appellant did not contest. Moreover, since the description does not provide any additional information that would be applicable to any other scale

of production than a laboratory scale, a skilled reader would not have any reason to expect that such reaction conditions for a laboratory scale would be applicable also for other scales of production up to an industrial plant. Even more, an organic chemist well-acquainted with reactions commonly used in processes for synthesising organic compounds and with the industrial implementation of such processes would realise that in the implementation of chemical processes on an industrial scale the transfer of, for example, mass and heat is scale dependent, since they behave differently on a small scale, such as in laboratory or in pilot plants, in comparison to a large scale, such as in large industrial production units.

2.1.6 Thus, in the absence of any disclosure in the application as filed that the parameters and reaction circumstances disclosed in phases a) to e) of example 1 are applicable for any scale of production, a skilled reader would derive therefrom that the reaction circumstances described in that phases a) to e) were disclosed only for conducting the reaction on a laboratory scale and that it could not be directly and unambiguously derived therefrom that such reaction circumstances would necessarily apply to large scale production of L(-)cloperastine hydrochloride or fendizoate.

2.2 Since, thus, the processes of Claims 1 and 2 were not unambiguously derivable for all possible scales, Claims 1 and 2 are amended in such a way that subject-matter extending beyond the content of the application as filed is added, contrary to the requirement of Article 123(2) EPC

3. Already for this reason alone, the set of claims according to the main and sole request is not allowable.

## Order

## For these reasons it is decided that

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin A. Nuss