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15

Aktenzeichen / Case Number / N° du recours : T 289/84

Anmeldenummer / Filing No / N° de la demande : 80 104 029.6

Veröffentlichungs-Nr. / Publication No / N° de la publication : 22 578

Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : 3-Amino-pyrazoline derivatives and pharmaceutical compositions containing them

Klassifikation / Classification / Classement : A 61 K 31/415

ENTSCHEIDUNG / DECISION
vom / of / du 10 November 1986

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent /
Titulaire du brevet : Wellcome Foundation Ltd.

Einsprechender / Opponent / Opposant :

Stichwort / Headword / Référence :

EPÜ / EPC / CBE Article 54

Kennwort / Keyword / Mot clé : "Novelty - Technical Feature Expressed in Functional Terms
- Allowability of a Claim to a Topical Formulation Although Other Formulations with Same Active Ingredient Known"

Leitsatz / Headnote / Sommaire

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Case Number : T 289 /84

D E C I S I O N
of the Technical Board of Appeal 3.3.1
of 10 November 1986

Appellant : The Wellcome Foundation Limited
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Decision under appeal : **Decision of Examining Division** 001 **of the European Patent Office dated** 17 July 1984 **refusing European patent application No.** 80 104 029.6 **pursuant to Article 97(1) EPC**

Composition of the Board :

Chairman : K. Jahn
Member : F. Antony
Member : R. Schulte

I

Summary of Facts and Submissions

1. European patent application No. 80 104 029.6, filed on 11.07.80 with USA priority of 13.07.79, and published on 21.01.81 under publication number 22578, was refused by a decision of the Examining Division 001 dated 17.07.84. The said decision was based on twelve claims, of which the first eleven were directed to a pharmaceutical formulation comprising (together with a carrier) a compound belonging to a generally known class of compounds of formula I, whereas Claim 12 contained an enumeration of twelve individual compounds of the said class, claimed **per se** as novel.

II. The reasons of the above decision were essentially as follows: The pharmaceutical formulations of Claim 1 are not novel; to be considered novel, they would have to be novel as such, regardless of their intended use.

Compounds of formula I, as well as their use in pharmaceutical formulations containing polyethylene glycols and water being known from

(A) US-A-3 927 025

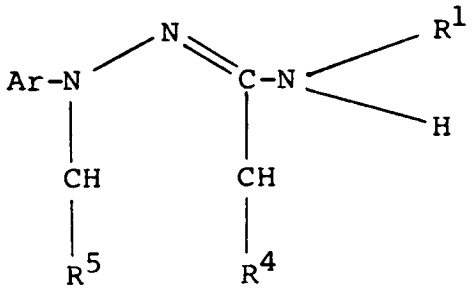
(even though their **topical** applicability is not mentioned in the prior art), the required **per-se** novelty of the claimed formulations could only be established by means of a technical feature clearly distinguishing them from that prior art. In contrast thereto, the functional feature "... adapted for topical administration" does not unambiguously imply a composition different from, e.g., an injectable formulation; for, an injectable solution is also topically applicable, it being unnecessary to "adapt" it to such application by any modification of its form or composition.

In a previous communication, the Examining Division had expressly accepted the existence of an inventive step and suggested possible amendments to overcome the lack-of-novelty objection, but as the Applicants were unwilling to limit the claims accordingly, the Examining Division saw no way to avoid refusal of the application.

III. On 06.09.84 the Applicants (Appellants) filed a Notice of Appeal against the above decision, paying the prescribed fee at the same time. The Grounds of Appeal were submitted on 26.11.84. After the Board raised objections in a communication, the Appellants have, on 09.08.85, submitted amended Claims 1, 6 and 12 - thus maintaining Claims 2 to 5 and 7 to 11 of the set of claims rejected by the Examining Division - and a revised description. After a personal consultation with the Rapporteur they have filed further arguments in support of the resulting claims.

IV. Claim 1 now reads as follows (the underlined passages showing the additions to the version rejected by the Examining Division):

"A pharmaceutical formulation, characterised in that the formulation is adapted for **only** topical, **to the exclusion of oral and injectable** administration and comprises a heterocyclic compound of formula (I)



(I)

wherein,

Ar is selected from pyridyl or phenyl, each of which may be optionally substituted in one or two positions in the ring by the same or a different substituent, said substituent being selected from trifluoromethyl, fluoro, chloro, bromo and iodo;

R^1 is selected from hydrogen and acyl having from 1 to 4 carbon atoms; and
R^4 and R^5 are the same or different and each is selected from hydrogen and alkyl having from 1 to 4 carbon atoms;

or a pharmaceutically acceptable acid addition salt thereof, together with a pharmaceutically acceptable carrier therefor."

Independent Claim 12 reads:

"A heterocyclic compound of formula (I), characterised in that the compound is selected from
3-amino-1-(p-fluorophenyl)-4-methyl-2-pyrazoline
3-amino-1-(m-chlorophenyl)-4-methyl-2-pyrazoline
3-amino-1-(p-chlorophenyl)-5-ethyl-2-pyrazoline
3-amino-1-(p-fluorophenyl)-5-methyl-2-pyrazoline
3-amino-1-(p-chlorophenyl)-4-methyl-2-pyrazoline
3-amino-1-(m-chlorophenyl)-5-methyl-2-pyrazoline
toluene-p-sulphonate."

V. The Appellants request that the impugned decision be set aside and a patent be granted on the basis of the present twelve claims.

Reasons for the Decision

1. The appeal complies with the requirements of Articles 106 to 108 and Rule 64 EPC; it is, therefore, admissible.

2. There can be no formal objection to the present version of the claims: Claim 1 differs from the one rejected by the Examining Division only insofar as it contains the disclaimer indicated by the underlined portions shown above. This disclaimer was added in view of the prior art (A) and is thus formally permissible.

Claims 2 to 5 and 7 to 11 are unchanged.

Claim 6 results from previous Claim 6 through cancellation of the second to seventh of the seven compounds enumerated therein.

Claim 12 is arrived at from previous Claim 12 (original Claim 14) by cancellation of all but six of the compounds enumerated therein. While previous Claim 12 was deleted in the Grounds of Appeal submitted 26.11.84 (page 1, last line), its reinsertion is unobjectionable in the absence of an express or implicit waiver at that time.

3. It being non-controversial that pharmaceutical formulations comprising compounds of formula I together with pharmaceutically acceptable carriers therefor are known, novelty - if existing - would have to rest entirely upon the claimed formulations being "adapted for only topical, to the exclusion of oral and injectable administration".

3.1. So that the afore-quoted phrase intended to serve as distinguishing feature is capable of establishing novelty in the sense of Art. 54 EPC, the cited prior art documents (taken singly) must not already disclose to the expert reader the topical administration of a pharmaceutical formulation comprising a compound of formula I.

3.1.1. Document (A) discloses pharmaceutical formulations comprising compounds of formula I, which are said to be antispasmodic agents. Administration of such formulations is mentioned in column 3, lines 4 to 9, and in column 5, line 40, to column 6, line 48. The first-mentioned passage being of a very general nature, not disclosing any particular mode or form of administration, only the last-mentioned passage requires detailed analysis :

Peroral (=oral) administration ("p.o.") is expressly referred to in column 5, line 63, and column 6, lines 1 and 5. It is also exemplified by reference to tablets, pills, coated pills and capsules in column 6, lines 12 to 13, 20 and 31 to 46. Reference to injection is made in column 6, lines 2 ("s.c." = subcutaneous), 14 ("injectable") and 25.

The mentioning of suspensions and emulsions (column 6, lines 13 to 14 and 25 to 26), when read out of context, is "neutral", in the sense that it could conceivably refer to oral as well as to topical preparations; but read in context it will be understood by the expert as pointing to only the former, for two reasons :

In column 6, lines 11 to 14, it is said that the compositions may be finished "in solid form" - then follow as examples typical oral preparations (tablets etc.) - "or liquid, e.g. suspensions, emulsions, or ..."; this suggests to the reader suspensions or emulsions for **oral (as opposed to topical)** use. In column 6, lines 24 to 27, it is stated that preferably the amounts of active component "per unit, i.e. ... per cc of suspension or emulsion" are in a certain range expressed in milligrams; this, together with the dosage ranges mentioned at various places between column 5,

line 52, and column 6, line 5, points likewise towards systemic (as contrasted to topical) use - it being unusual to give such dosage ranges for topical preparations.

Concerning activity, (A) discloses use of the concerned active compounds as **antispasmodic** agents. In its section dealing with antispasmodic drugs, the standard text book

(F) "Remington's Pharmaceutical Sciences", 16th Edition (1980),

after a passing reference to various selective drugs - among which are "local anesthetics for some localized neurally mediated spasms" - states that the term "antispasmodic drugs" should be reserved for those drugs that relax smooth muscle nonselectively (page 860, lefthand column, lines 16 to 18 of section "Antispasmodic Drugs"). Following this, it gives typical examples of such nonselective antispasmodic drugs, all for systemic application. This is consistent with the afore-mentioned reference to **smooth** muscles, because the location thereof in the body would practically rule out topical administration thereto. Thus the expert will not consider such application when reading about antispasmodic activity of certain compounds. In particular, he will not consider topical application in the case of (A), where the **in-vivo** experiments of column 5, line 66, to column 6, line 5, report inhibition of electroshock spasm by oral or subcutaneous treatment, and of nicotine toxicity inhibition by oral treatment with the active compounds in question.

3.1.2. Document

(D) Prostaglandins, Vol. 16 (1978), 179-186, deals exclusively with application of one particular active compound of formula I by way of lung perfusion (see top of page 180), i.e. systemically.

Reference

(E) Biochemical Pharmacology, Vol. 28 (1979), 1959-1961

compares the anti-inflammatory activity of one particular active compound of formula I with known anti-inflammatory drugs, whereby "each drug was given orally" (page 1960, penultimate paragraph, line 7), although in some experiments one of the comparative drugs was also given by another - equally systemic - route, viz. intra-muscularly.

3.1.3. As can be seen from the above analysis, none of the references (A), (D) and (E) contains any basis for the expert to interpret it in the sense that also **topical** administration is taught. References

(B) DE-A-2 727 706 and

(C) Chem. Abstr. 54 (1960), 1501 b-f,

are not relevant to the **in-vivo** administration of compounds of formula I. Accordingly, the above condition for the existence of novelty is met.

3.2. It having been established that none of the cited prior-art documents discloses to the expert reader **topical** administration of the compounds in question, the Board has also investigated whether adaptation to (only) topical use is a true technical distinguishing feature which establishes a material difference.

Document (A) discloses as suitable carrier, e.g., water (column 6, line 11); i.e. as formulations, compositions which are essentially aqueous solutions - for instance, injection solutions -, suspensions or emulsions (column 6, lines 1 to 14) of active compounds of formula I. The topical compositions falling within the claimed range which are most closely related to injectables are eye drops. If the expert

should want to prepare such eye drops, he will not simply dissolve an active compound in sterile water (sterility being a generally known requirement for eye drops as well as for the injection solutions disclosed in (A)); rather he will adapt the aqueous solution to the particular topical administration desired, viz. he will include certain additives to adjust tonicity and pH, stabilize the preparation, etc. (see extracts from British Pharmacopoeia and U.S. Pharmacopoeia filed 26.11.84, page 565, righthand column, paragraph 2, and, respectively, page 1027, righthand column, paragraph 4 from the bottom). It is irrelevant that these additives are generally used in fairly small quantities: they establish a material difference; hence so does the adaptation to topical administration, which is therefore a material feature, though one expressed in functional terms.

The existence of a material difference is also confirmed when the concrete excipients other than water mentioned in Examples 40 to 43 (pages 19 to 20) and on page 26, lines 17 to 22, of EP-A-22578 are compared with those specifically referred to in (A) - column 6, lines 9 to 11 and 35 to 45 -; no comparable specific disclosure being contained in any of the other literature references.

3.3. Finally, as a kind of safety check for novelty, the Board has also satisfied itself that none of the formulations disclosed in the citations does in fact materialize the proposed distinguishing feature - irrespective of the envisaged prior-art use of the concerned formulation. This criterion would certainly not have been met by the previous intended distinguishing feature of "suitability" for topical administration. As the Appellants correctly point out (page 5, paragraph 1, of their Grounds of Appeal dated 26.11.84), the words "suitable for" express that something can be used for a given purpose, although it is not necessarily

particularly appropriate for that purpose. Thus, for instance, an aqueous injection solution as disclosed in (A) would generally be **suitable** for topical administration, e.g. to the human skin or eye.

On the other hand, such an injection solution is not adapted for such a topical administration : As pointed out before, the teaching of a patent specification such as that of (A) is addressed to the expert pharmacist, and no such expert, when instructed to prepare, e.g., an injection solution, would realistically conceive preparing of a formulation adapted for topical administration, such as for eye drops. While in certain respects the requirements for eye drops are less stringent than for injection solutions - injection solutions must be both sterile and pyrogen-free, while only the former requirement applies to eye-drops - in other respects even more care is necessary for eye drops than for injection solutions (see (F), pages 1502-1504), but one example being a narrow pH range to avoid strong discomfort (page 1504, righthand column, lines 15 et seq.). An expert instructed to prepare an injection solution will therefore, on the one hand, not pay the same degree of attention to factors, such as pH, which are particularly important for a formulation to be adapted for use as eye drops; on the other hand, he will - unnecessarily from the point of view of adaptation for ophthalmic use - apply great care to make his solution pyrogen-free. A formulation intended for use as injection solution will therefore, in reality, never be adapted for use as eye drops, even though both, the injection solution and the eye drops, are in essence sterile aqueous solutions of the active compound concerned.

A slight difficulty was at one point seen in that, by the Applicants' own admission (page 6, lines 6 to 5 from the bottom, of the Grounds of Appeal dated 26.11.84), a topical formulation (i.e., in terms of the claim, a formulation

adapted for topical administration) is only "**likely** to contain pyrogenic material", in other words, it may in fact happen to be pyrogen-free. In such a case, **disregarding the other prerequisites for a formulation to be adapted for administration as eye drops**, there appeared to be a danger of marginal overlap. This being a borderline case, the Board has therefore, for better clarity, suggested, and the Applicants have agreed, to specify the claimed formulations as adapted for **only** topical administration, specifically excluding formulations which would at the same time be adapted for, e.g., oral and injectable administration. Certainly with this disclaimer, superfluous as it might possibly be, the above test is met, thus the claimed formulations are properly delimited vis-à-vis the known formulations, none of which can be said to have been adapted for (only) topical administration.

3.4. Summarizing the considerations on novelty, the following can be stated: The fact that a chemical compound and pharmaceutical formulations containing the same as an active ingredient are known does not rule out a claim directed to a specific mode of formulation not disclosed by the prior art (in the present case: to a formulation adapted for - only - topical administration), as opposed to only a use claim (in the case of pharmaceutical uses: in the form approved by the Englarged Board; see OJ 3/1985, 64-66).

4. The existence of an inventive step with respect to at least Claim 1 (thus at least indirectly for dependent Claims 2 to 11 as well) was expressly accepted by the Examining Division (see Communication of the Examining Division of 27.07.83, page 2, second sentence of numbered item 3). This opinion was based on the Applicants' arguments (writ dated 18 March 1983, page 5 **et seq.**) that a **topical** anti-inflammatory activity of the compounds of formula I could not be expected on the basis of the cited prior art, particularly (E).

4.1. In the same vein, in their letter received 18.06.86, the Appellants have argued that an expert would not seriously consider trying topical administration of the compounds in question for the spasmolytic indications mentioned in (A), because spasmolytic agents serve to prevent spasms in smooth muscle tissue of the blood vessels, heart muscle, respiratory tract etc. (page 2, paragraph 3), to which sites a topical administration is virtually excluded. This presently irrefutable statement is consistent with the conclusions from the standard textbook (F) reached in the last paragraph of subsection 3.1.1. hereinabove.

4.2. Whereas document (A), in view of the detailed disclosure therein, has been in the foreground of discussions so far, document (E) is, from a systematic point of view, the closest art. While the arguments of the two preceding paragraphs were based upon the problem of providing compositions for **another** mode of administration, the solution of a more ambitious problem, starting from (E), can be accepted in view of the Appellants' statements in the two final paragraphs on page 2 of their said letter received 18.06.86, viz. providing a **safer** mode of administration; for they have stated that, unexpectedly, the ratio of effective to toxic dosage of the compound of Claim 6 is 12.5 to 50 in the case of topical, against 2.5 in the case of systemic administration. While the afore-quoted results have been given in somewhat vague terms, so that the Board would be reluctant to base a finding of inventive step solely upon them, they do contribute to strengthen the conclusions of the preceding paragraphs.

4.3. All taken together, therefore, the Board is satisfied that the subject-matter of Claim 1 does involve an inventive step.

5. The objection under Article 84 and Rule 29(3) EPC raised by the Examining Division against Claim 6 in its then version in the said Communication of 27.07.83 is clearly avoided by present Claim 6, mentioning but a single compound. In view of the above, Claims 1 to 11 meet all the requirements of the Convention and are thus allowable.

6. Claim 12, in its then form, was also considered objectionable by the Examining Division on the same legal basis. Certainly in its present form, Claim 12 is not so objectionable; for, all the compounds enumerated have in common the structural elements of 3-amino-1-halogenophenyl-4-or-5-methyl-2-pyrazolines. Reference is also made to a previous decision of this Board, T 156/82 of 09.01.84 (unpublished), from which it can be deduced that an enumeration of a plurality of compounds in one claim need not necessarily be objectionable under Article 84 or Rules 29 or 31 EPC, as long as the necessary perspicuity ("Übersichtlichkeit") is guaranteed.

7. However, Claim 12 (then numbered 14) was also objected by the Examining Division on the basis that the novel compounds thereof be obvious modifications of the compounds known from Prostaglandins, Volume 18, 179-187, and Biochem. Pharmacol. 28(1979), 1959-1961, and would only meet the requirements of Article 56 EPC if they should exhibit surprising properties when compared with those known compounds (Communication of 21.09.82, page 3, numbered paragraph 6). In their reply received 21.03.83 (page 12, third paragraph), the Applicants

asked for leave "to defer this point until a final decision has been made about the scope of the main claim". Since then, this point has not been re-raised. Thus, the novelty of Claim 12 has implicitly been acknowledged by the Examining Division, but it remains to be examined whether this claim involves an inventive step. Insofar as Claim 12 is concerned, there has therefore been no full first-instance examination

yet. In order to guarantee such examination without loss of instance, the Board considers it appropriate to make use of the power granted to it under Article 111(1) EPC and to remit the case to the Examining Division for further prosecution.

8. Also the amended description submitted 09.08.85 still requires examination.

Order

For these reasons,

it is decided that:

1. The impugned Decision of the Examining Division is set aside.

2. The case is remitted to the Examining Division for further prosecution on the basis of the following documents:

   (a) Claims 1, 6 and 12 as submitted on 09.08.85;
   (b) Claims 2 to 4 as originally filed;
   (c) Claims 5 and 7 to 11 as submitted on 21.03.83;
   (d) description with amendments as submitted on 09.08.85.

Delivered 12.11.86