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D E C I S I O N
of 4 December 1997

Case Number: T 0188/95 - 3.3.2

Application Number: 86200589.9

Publication Number: 0200252

IPC: A61K 31/635

Language of the proceedings: EN

Title of invention:
Tablets comprising trimethoprim and a sulfonamide

Applicant:
YAMANOUCHI EUROPE B.V.

Opponent:
-

Headword:
Tablets/YAMANOUCHI

Relevant legal provisions:
EPC Art. 56
EPC R. 67

Keyword:
"Problem invention (no)"
"Inventive step (yes)"
"Procedural violation (no)"

Decisions cited:
T 0018/81

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0188/95 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 4 December 1997

Appellant: YAMANOUCHI EUROPE B.V.
Elisabethhof 19
P.O. Box 108
NL-2350 AC Leiderdorp (NL)

Representative: -

Decision under appeal: Decision of the Examining Division of the European Patent Office posted 16 September 1994 refusing European patent application No. 86 200 589.9 pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent application No. 86 200 589.9 filed on 7 April 1986 and published as EP-A-0 200 252 was refused by the decision of the Examining Division dated 16 September 1994. The decision was based on claims 1 to 12 as originally filed for all designated contracting states other than Austria, with the corrections to claims 1 and 9 requested with the Applicant's letter of 12 June 1990, and claims 1 to 12 for Austria filed on 27 November 1986.

Independent claims 1 and 10 were worded as follows:

"1. Tablets containing trimethoprim or a salt thereof and a sulfonamide or a salt thereof in a ratio between 1:20 and 20:1, the total weight of said ingredients being from 80 to 98% of the total weight of the tablet, characterized in that they comprise an ion exchanger of the artificial resin type.

10. Process for the preparation of tablets as defined in claim 1, characterized in that a mixture is made, comprising trimethoprim or a salt thereof and a sulfonamide or a salt thereof, the mixture is granulated with a suitable liquid, the granulate is mixed with one or more other ingredients and tablets are compressed from the mixture and an ion exchanger of the artificial resin type is added during the preparation of the granulate and/or added to the granulate."

Claims 1 and 10 were followed by dependent claims 2 to 9 and 11 to 13 relating to specific embodiments of the respective independent claims.

II. The stated ground for the refusal was lack of inventive step of all claims. The Examining Division considered GB-A-2 067 900 (document 1) to be the closest state of the art and found that the claimed tablets in the application differed from those disclosed in (1) by the mere fact that crosslinked (insoluble) polyvinylpyrrolidone, used in the known tablets as a strongly swelling disintegrating agent, had been replaced by an ion exchanger of the artificial resin type.

It was already stated in the description of the present application as filed (cf. page 1, paragraph 4) and repeated by the Appellant in his submissions that the use in the prior art of a strongly swelling disintegrating agent was to be considered as disadvantageous insofar as it was responsible to render this kind of tablets slimy and sticky already in contact with a small amount of water in the mouth thereby causing an unwanted bitter aftertaste on administration.

Thus, the technical problem was defined in the impugned decision (see Reasons; point 3) as that of "making tablets based on a high amount of the active ingredients trimethoprim and a sulfonamide which dissolve quickly in water and do not leave a bitter aftertaste."

In the opinion of the Examining Division, the skilled person seeking a solution to this problem in the state of the art would have known from Pharmaceutica Acta Helvetiae, 57, 1982, pp. 131-135 (document 5), that an ion exchanger of the artificial resin type, such as Amberlite IRP 88®, was a particularly suitable disintegrating agent for making certain fast-disintegrating tablets containing more than 80% of a water insoluble ingredient, more specifically

phenacetin. He would also have obtained from Drug Development and Industrial Pharmacy, 6, 511-536, 1980, p. 527 (document 6), all the relevant information he needed about the swelling properties of the commonly used disintegrating agents, including Amberlite IRP 88^{R}.

In the light of the above, the Examining Division took the view that it was a matter of routine for the skilled practitioner to solve the technical problem by replacing crosslinked polyvinylpyrrolidone used in (1) as the disintegrating agent with an ion exchanger of the artificial resin type which had already been suggested in (5) for a similar purpose.

III. An appeal against the above decision was filed by the Applicant on 16 November 1994 and oral proceedings took place on 4 December 1997. During presentation of his arguments in support of the appeal both in the written procedure and at the oral proceedings, the Appellant, starting from (1) or GB-A-149 967 (document 2) as the closest state of the art, arrived at a technical problem which was substantially identical with that adopted by the Examining Division.

The Appellant essentially argued that it was solely the contribution of the present inventors to have recognised the bitter aftertaste as a serious drawback of the known tablets resulting from the use of a strongly swelling disintegrating agent in the prior art of (1) and (2). Since the disintegration properties of the known tablets were excellent, the skilled person, faced with the instant technical problem, would have thought of replacing the excipients used in the prior art as the wet binding agents to avoid stickiness, or would have thought of different taste-masking techniques to get rid of the bitter aftertaste, rather than of replacing the disintegrating agent.

Moreover, the question to be answered was not whether the skilled person could have modified in view of the teaching of (5) the known composition of the tablet but whether he would have done so in the expectation of a technical benefit. This question had to be denied since the state of the art was entirely silent about a correlation between the swelling properties of the disintegrating agent and the occurrence of a bitter aftertaste in tablets. The choice of another disintegrating agent having significantly different swelling properties to solve the technical problem was thus far from being obvious.

The Appellant requested that the impugned decision be set aside and a patent be granted on the basis of the two set of claims refused by the Examining Division (see paragraph I above) and the original description with the corrections at line 29 on page 1 and in Example 1 submitted during oral proceedings before the Board of Appeal.

IV. The Appellant further requested the reimbursement of the appeal fee in view of alleged procedural violations and submitted in support of this request essentially the following arguments:

Although the correct technical problem had been introduced by the Appellant already at a very early stage in the proceedings, he felt that it was totally ignored during examination of the present case and was adopted by the Examining Division for the first time in the impugned decision. The Appellant considered this as indicative of the fact that the Examining Division had failed to pay due attention to the arguments and observations provided on his part in support of inventive step during the whole proceedings and, hence, contravened the party's right to be heard (Article 113(1) EPC).

The Appellant contended also that document (6), though supplied by himself in support of his case, was used against him without giving him a sufficient opportunity to make observations and referred in this context to Decision T 18/81.

Reasons for the Decision

1. The appeal is admissible.

2. The corrections of errors in the original claims concern deletion of the erroneous insertion "for the preparation of tablets" between "Tablets" and "containing" in line 1 of the precharacterizing portion of claim 1 and rectification of a linguistic error in claim 9. The corrections in the description pertain to the replacement of the wrongly cited unit "m" (metre) in the reference to the prior art of (2) at line 29 on page 1 with the correctly cited unit "micrometer", and to the insertion of the missing unit "g" following the numerical value of 28.8 in Example 1.

   All requested corrections are obvious in the sense of Rule 88, 2nd sentence, EPC, and are therefore acceptable.

3. Tablets containing an admixture of 2,4-diamino-5-(3,4,5-trimethoxybenzyl)pyrimidine (trimethoprim) and a sulfonamide as the active ingredients in a proportion of more than 80% of the total weight of the tablet are already known in the state of the art. The high proportion of the said admixture is desirable and necessary to facilitate the preparation of tablets which contain the required high dosage of up to 900 mg

of the active ingredients but which are nevertheless, as far as their size and physical properties are concerned, suitable for oral administration without undue discomfort to patients.

Document (2) discloses such tablets comprising from 80 to 98% by weight of an admixture of trimethoprim and a sulfonamide, in which the admixture has a particle size, defined in terms of "weight median diameter", of less than 40 micrometer and which include among other conventional excipients, such as a wet binding agent, a strongly swelling disintegrating agent having a swelling capacity greater than 5 ml/g. The swelling capacity of the disintegrating agent is defined in (2) as the volume (ml) to which 1g of a tablet containing 95% (w/w) of the dry disintegrating agent and 5% (w/w) of polyvinylpyrrolidone will swell when in contact with an excess of water at a temperature of 21°C.

The tabulated test results in the table on page 5 of (2) in connection with the corresponding statements in the specification, in particular at lines 14 to 30 on page 2 and at lines 2 to 6 on page 5 relating to the said test results, provide the skilled reader with the teaching that the use of a disintegrating agent with the indicated strong swelling capacity was regarded in (2) as crucial to produce tablets having a satisfactorily short disintegration time in water between about 1 and 3 minutes, in spite of their high content of the active ingredients which both are highly insoluble in water.

Document (1) which was published later than document (2) contains in the introductory part a reference to document (2) and may be considered as relating to a specific embodiment of the more general technical teaching given in (2). Thus, document (1) discloses in the only example included in the

specification a tablet comprising 93% by weight of an admixture of trimethoprim and sulfamethoxazole in combination with 5.5% by weight of crosslinked insoluble polyvinylpyrrolidone (hereinafter referred to under the trade name Polyplasdone^{R}, see document (5), page 1, paragraph 2.1) as the disintegrating agent and for the remainder certain other conventional excipients such as soluble polyvinylpyrrolidone as a wet binding agent.

It is derivable from the swelling properties listed in (6) for a respectable number of pure tablet disintegrants that Polyplasdone^{R} reaches its maximum swelling capacity of 112% within a period of time of 9 minutes with a swelling capacity of 39% within the first minute, and appears thus with respect to its swelling properties entirely comparable to certain other strongly swelling disintegrating agents expressly mentioned in (2), for example sodium carboxymethyl starch known under the common name Primojel^{R} (see (6), page 527, Table 6).

Tablets disclosed in (1) show a disintegration time of less than 1 minute.

4. The tablets disclosed in (1) and (2) exhibit admittedly satisfactory properties, as far as their size, their high proportion of the active ingredients combined with reasonably short disintegration times in water and their other physical properties such as hardness, abrasion and friability are concerned. Notwithstanding this, the Appellant sees a serious drawback of the known tablets in the fact that the strongly swelling disintegrating agent used in the state of the art becomes slimy and sticky already in contact with a small amount of liquid in the mouth. This property of the disintegrating agent was realized by the Appellant to be responsible that the resulting tablets may

develop a lingering bitter aftertaste on administration which originates from the inherent bitter taste of trimethoprim and the sulfonamide and is met with some measure of discomfort to patients.

In the light of the closest state of the art, such as illustrated by the documents (1) and (2), the technical problem may thus be seen in providing tablets which meet with regard to their size, their high proportion of the active ingredients trimethoprim and the sulfonamide, their short disintegration time in water and their other physical properties at least the standards achieved in the cited state of the art, but which do not develop a bitter aftertaste on administration.

According to the application it is proposed to solve this technical problem essentially by replacing the strongly swelling disintegrating agent used in the prior art with an ion exchanger of the artificial resin type, typically an Amberlite-type resin, optionally in combination with other excipients.

In view of the content of up to 98% of the active ingredients (cf. Example 18), disintegration times in the range of from less than 15 seconds (cf. Examples 17, 19) to less than 60 seconds maximum, and the good physical properties reported for the tablets produced in accordance with the examples included in the present application and, moreover, in view of the rather low maximum swelling capacity of 57% after 15 minutes with only 17% within the first minute reported in (6) for the disintegrating agent preferably used in the said examples, the Board has no reasonable doubts that the technical problem defined above has in fact plausibly been solved.

5. After examination of the citations uncovered by the

search report and those introduced by the Appellant during the proceedings, the Board has reached the conclusion that none of them discloses a tablet including all the technical features stated in claim 1. Since this has never been disputed, there is no need for further detailed substantiation of this matter. Therefore, the subject-matter as set forth in the present claims is deemed to be novel within the meaning of Article 54(1) EPC.

6. The issue in the present case is therefore that of inventive step. From the assessment of this matter, the following points emerge:

6.1 The Appellant also argued at the oral proceedings that it was solely the merit of the present inventors to have recognised for the first time the technical problem actually forming the basis of the present application and this should at least contribute to the acknowledgment of an inventive step in the present case.

It is true that none of the cited documents discloses or otherwise explicitly refers to the drawback of the known tablets resulting from their bitter aftertaste on oral administration. Notwithstanding this, any person taking such a tablet would, in the Board's judgement, normally immediately realize their bitter aftertaste as a discomfort and drawback. Since the overcoming of such a perfectly obvious, directly identifiable drawback and the achievement of an improvement resulting therefrom must be considered as the normal task of the skilled person, the Board cannot share the Appellant's view that a contribution to the inventive step could possibly be seen in the present case already in the perception of the particular technical problem as defined in paragraph 4 above.

6.2 It remains therefore to be examined whether the claimed solution is obvious to a skilled person in view of the prior art.

First of all it should be noted that there is no direct correlation derivable from the state of the art available in the proceedings between the bitter aftertaste of a tablet of any kind and the particular properties of the tablet disintegrant used. Moreover, since the bitter aftertaste of the known tablets has its origin clearly in the extremely bitter taste of both the active ingredients, trimethoprim and the sulfonamide, it was, in the Board's judgement, at the date of priority of the present application not readily to be expected for a skilled person that such bitter aftertaste could successfully be avoided just by replacing the disintegrating agents used in the state of the art which are, according to the Appellant's assertion during oral proceedings, in contrast to the active ingredients entirely tasteless.

Thus, it cannot be considered obvious that the instant technical problem could only be solved by replacing the disintegrating agent. For one thing, various ways of solving the problem posed presented themselves to the person skilled in the art. For example, there was the frequently used and, in the Board's opinion, more obvious possibility of using certain well known taste-masking techniques to get rid of the bitter aftertaste, such as encapsulation or entrapment of the active ingredients, or covering the tablets with a tasteless or good tasting coating, or including certain sweeteners in the tablet mass. The Board concurs also with the Appellant's opinion that another realistic alternative the skilled person could have thought of was the possibility of avoiding stickiness by exchanging certain excipients of the tablets which have inherently water binding and sticky properties such as,

for example, the wet granulation binding agents used for the preparation of the tablets disclosed in (1) and (2), rather than by replacing the disintegrating agents.

6.3 From document (5) an ion exchanger of the artificial resin type, more specifically Amberlite IRP 88^{R}, is indeed known as the disintegrating agent for the preparation of certain fast-disintegrating tablets containing phenacetin, which is also sparingly soluble in water, as the active ingredient in a proportion of about 80% by weight. Any indication that this particular disintegrant is to serve to avoid a bitter aftertaste of the tablet is lacking, however. Moreover, it appears also necessary to point to the substantial difference in structure which exists between phenacetin, on the one hand, and trimethoprim and compounds belonging to the class of the sulfonamides, on the other.

What basically distinguishes the disintegrant Amberlite IRP 88^{R} from those used in the cited state of the art as well as from essentially all other disintegrating agents alternatively suggested in (5) for the same purpose as Amberlite IRP 88^{R}, for example Primojel^{R}, Polyplasdone^{R}, Ac Di Sol^{R}, are its moderate swelling properties reported in (6) and already mentioned in paragraph 4 above.

In this respect it appears worthwhile to note that both the documents (1) and (2) impressively demonstrate the considerable effort that was necessary in the state of the art to obtain tablets containing trimethoprim and a sulfonamide having the desired short disintegration time and adequate physical properties in spite of their high content of the active ingredients. The success achieved in this respect can be clearly attributed in the cited documents to the use of a strongly swelling

disintegrating agent. Thus, in the Board's opinion, the skilled person faced with the instant technical problem would have been rather reluctant to jeopardize the progress achieved in the state of the art by using a disintegrant having swelling properties, which are distinctly different from those used in (1) and (2) as has Amberlite IRP 88^{R}.

Moreover, the skilled person would learn on closer inspection of the data provided in Table 4 on page 135 of document (5) that the shortest disintegration time of phenacetin-containing tablets is achieved by using Ac Di Sol^{R} as the disintegrating agent followed by Amberlite IRP 88^{R}. However, knowing from the prior art of (1) and (2) the relevance of the strong swelling capacity of the tablet disintegrant to the disintegration time and the other physical properties of a tablet containing trimethoprim and a sulfonamide, he would also scrutinize the swelling properties of the disintegrants listed in (6) to learn that Ac Di Sol^{R} ensures not only the shortest disintegration time but at the same time has the highest maximum swelling capacity of 210% in that list, and other disintegration agents mentioned in (5), for example Primogel^{R} and Polyplasdone^{R} belong to the class of strongly swelling disintegrating agents as well, in sharp contrast to Amberlite IRP 88^{R}.

In view of the foregoing the Board considers that the skilled person could not expect the problem defined hereinbefore to be solvable in its entirety just by using the particular disintegrating agent chosen in the application. Apart from the fact that the prior art provides absolutely no indication that the bitter aftertaste was in any kind related to the properties of the disintegrating agents used in the known tablets, the skilled person had to entirely ignore the correlation which has been established in the closest

state of the art of (1) and (2) between the swelling properties of the disintegrant used and the disintegration time and the physical properties of the resulting tablets, in order to arrive at the solution proposed in the application.

Moreover in the Board's judgment the skilled person could on the basis of the prior art also not expect that the claimed tablets in the application would with respect to their desirably short disintegration time in the range of less than 15 to less than 60 seconds, as already mentioned in paragraph 4 above, compare favourably with those disclosed in the state of the art of (1) and (2).

6.4 In conclusion, the teaching of the application under consideration cannot be considered as obvious within the meaning of Article 56 EPC, whether expressed in accordance with independent claims 1 and 10 or their sub-claims, and consequently involves an inventive step.

7. Following from Rule 67 EPC reimbursement of the appeal fee is due in cases in which the Board of Appeal deems the appeal to be allowable if "such reimbursement is equitable by reason of a substantial procedural violation."

The Board cannot recognise such a substantial procedural violation in the present case. First of all, the impugned decision and preceding proceedings, including the four communications issued pursuant to Article 96(2) and Rule 51(2) and the minutes of the oral proceedings, show that the Examining Division has prepared its negative decision to the Appellant so that he could not have been surprised and his right to be heard has therefore been observed.

As has been admitted by the Appellant himself, the arguments in the decision under appeal are based on a technical problem which has been adapted in order to take into account the arguments provided by the Appellant in his submissions during the proceedings and to which he fully agrees. The decision moreover enables the reader to follow a line of arguments for refusing the application and is essentially based on arguments which had already been communicated to the Appellant before the final decision was made. The Board therefore holds that the Examining Division did not use new arguments in its decision, and that Article 113(1) EPC has been observed.

The Board takes the view that, contrary to what the Appellant appeared to suggest in his submission during oral proceedings, Article 113(1) EPC is not violated by the mere fact that the Examining Division regarded certain arguments and submissions produced by the Applicant as possibly not relevant. Assessment of the relevance of arguments and evidence put forward is a matter for the instance which took the decision and, under Article 97(1) EPC, such a decision concerns the application itself and the invention involved, and not the Applicant's arguments.

8. As far as document (6) is concerned the Board cannot see that the Appellant has found himself in a position corresponding to that which formed the basis of Decision T 18/81 (OJ EPO 1985, 166). First of all, the minutes of the oral proceedings before the Examining Division submitted to the Appellant on 16 September 1994 (see especially the paragraph bridging pages 2 and 3) provide evidence that document (6) has been discussed during the said proceedings and, moreover,

that the Examining Division expressed to the Appellant its opinion about the non-relevance of this document to support an inventive step in the present case, so that he had, in the Board's judgement, the opportunity to make his observations.

Moreover, the Appellant himself has filed document (6) with the clear intention to provide information and evidence about the various swelling properties of certain known disintegrants, including the difference in this respect between Polyplasdone^{R} and Amberlite IRP 88^{R}. As this is virtually the only information which can be derived from (6), the Appellant cannot reasonably argue that the document was used against him in a surprising manner and that he had no opportunity to make observations on the information used. Finally, the decision under appeal cannot be considered to be essentially based on document (6), as it was the case with the documents introduced in the case of T 18/81.

9. In these circumstances, the Board sees no substantial procedural violations in the decision of the first instance, and therefore no valid reason for refunding the fee for appeal under Rule 67 EPC.

Order

For these reasons, it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to grant the patent in the following version:

   Claims 1 to 12 for all designated contracting states, Austria excepted;
   Claims 1 to 12 for Austria;
   both sets of claims as annexed to the decision under appeal;
   description pages 2, 3, 5 to 12, as originally filed;
   description pages 1 and 4, received during oral proceedings.

3. The request for reimbursement of the appeal fee is refused.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon