BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS

BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE

CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [X] To Chairmen

D E C I S I O N
of 16 January 1997

Case Number: T 0142/94 - 3.3.2

Application Number: 87309333.0

Publication Number: 0271193

IPC: A61K 31/485

Language of the proceedings: EN

Title of invention:
Controlled release hydromorphone composition

Patentee:
Euroceltique S.A.

Opponent:
BASF Aktiengesellschaft, Ludwigshafen

Headword:
Controlled release oral dosage/EUROCELTIQUE S.A.

Relevant legal provisions:
EPC Art. 56,

Keyword:
"Inventive step - yes - no clear pointer to the claimed solution"

Decisions cited:
-

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0142/94 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 January 1997

Appellant: (Opponent)
BASF Aktiengesellschaft, Ludwigshafen
-Patentabteilung - C6-
Carl-Bosch-Strasse 38
D-67056 Ludwigshafen (DE)

Representative:
-

Respondent: (Proprietor of the patent)
Euroceltique S.A.
122 Boulevard de la Petrusse
Luxembourg (LU)

Representative:
Ruffles, Graham Keith
MARKS & CLERK
57-60 Lincoln's Inn Fields
London WC2A 3LS (GB)

Decision under appeal:
Decision of the Opposition Division of the European Patent Office posted 6 December 1993 rejecting the opposition filed against European patent No. 0 271 193 pursuant to Article 102(2) EPC.

Composition of the Board:

Chairman: P. A. M. Lançon
Members: U. Oswald
R. E. Teschemacher

Summary of Facts and Submissions

I. European patent No. 0 271 193 was granted on the basis of two sets of claims (ten product claims for contracting states AT, BE, CH, DE, FR, GB, IT, NL and SE, and ten process claims for contracting state ES) contained in the European patent application No. 87 309 333.0.

Product claim 1 reads as follows:

"1. A solid controlled release, oral dosage form, the dosage form comprising a therapeutically effective amount of hydromorphone or a salt thereof in a matrix wherein the dissolution rate in vitro of the dosage form, when measured by the USP Paddle method at 100 rpm in 900 ml aqueous buffer (pH between 1.6 and 7.2) at 37°C is between 12.5% and 42.5% (by wt) hydromorphone released after 1 hour, between 25% and 55% (by wt) hydromorphone released after 2 hours, between 45% and 75% (by wt) hydromorphone released after 4 hours and between 55% and 85% (by wt) hydromorphone released after 6 hours, the in vitro release rate being independent of pH between pH 1.6 and 7.2 and such that the peak plasma level of hydromorphone obtained in vivo occurs between 2 and 4 hours after administration of the dosage form."

II. Opposition was filed under Article 100(a) against the granted patent by the Appellant. Of the numerous documents cited during the opposition proceedings, the following remain relevant to the present decision:

(3) M. Vater et al., "PHARMACOKINETICS AND ANALGESIC EFFECT OF SLOW-RELEASE ORAL MORPHINE SULPHATE IN VOLUNTEERS" : British Journal of Anaesthesia, vol. 56 (1984), pages 821 to 827,

(12) EP-A-0 032 004,

(13) R. J. Osborne et al., "Morphine intoxication in renal failure: the role of morphine-6-glucuronide" :British Medical Journal, vol. 292 14 June 1986, pages 1548/1549,

(15) E. J. Cone et al., "Urinary Excretion of Hydromorphone and Metabolites in Humans, Rats Dogs, Guinea Pigs, and Rabbits": Journal of Pharmaceutical Sciences, vol. 66, No. 12, December 1977, pages 1709 to 713.

III. The Opposition Division rejected the opposition under Article 102(2) EPC.

According to the decision under appeal the subject-matter of product claim 1 and dependent claims 2 to 10 as granted was novel and involved an inventive step.

The Opposition Division, decided that the controlled release oral dosage form defined in claim 1 solved the problem of providing therapeutic levels of hydromorphone *in vivo* over at least a period of 12 hours so that the dosage form could be administered on a twice daily basis.

Having regard to the cited prior art, the Opposition Division held that each of the numerous documents disclosing *in vitro* release and/or *in vivo*

pharmacokinetic profiles falling within the scope of those defined in claim 1 but disclosing specific types of drugs structurally and pharmacologically different from hydromorphone were not relevant.

Although document (12) described a particular matrix allowing the *in vitro* release of any given active ingredient over a period of from 5 to 15 hours, in the light of the disclosure of further prior art documents, it was clear that the *in vitro* release rate of an active ingredient did not necessarily correlate with its *in vivo* pharmacokinetic profile or its pharmacological effect.

In the view of the Opposition Division document (3) represented the closest prior art. This document related to the pharmacokinetics and the analgesic effect of a slow release oral formulation of morphine a compound which came structurally close to hydromorphone. However, in the absence of any disclosure as to a correlation between the plasma concentrations and the pharmacological effects of morphine, and by taking into account that in the light of document (13) this phenomenon could be explained by a therapeutically active metabolite of morphine which contributed to its long lasting analgesic effect, and in the absence of any evidence that hydromorphone had such therapeutically active metabolites, the Opposition Division took the view that there was no teaching in the prior art under which circumstances hydromorphone would show therapeutically effects over 12 hours. This conclusion was furthermore based on a statutory declaration by an expert.

IV. The Appellant lodged appeal against this decision and argued that the skilled person who desired to manufacture a controlled release drug formulation to obtain pain relief by using conventional methods and customary auxiliaries would inevitably arrive at the claimed invention.

A person skilled in the art clearly recognized that the desired therapeutic levels of a drug over a period of twelve hours could mainly be influenced by the choice of the matrix and the auxiliaries used in the composition and by subsequently adjusting the dissolution rate of the drug. Accordingly, the dissolution rate of the drug was the only factor the skilled person tried to control. Document (12) described without any restriction to a specific type of drug the use of matrices suitable for achieving any desired dissolution rate. It was furthermore possible to make assumptions about therapeutic levels of analgesically effective drugs based on the behaviour of codeine and morphine, drugs which structurally came very close to the now claimed hydromorphone and which showed similar physico-chemical properties, for example a very similar dissociation constant pK. According to a new document

(21) R. Kaiko et al., "Pharmacokinetik Characterization Of Controlled-Release Oral Codeine For Chronic Cancer Pain": Proceed. of Asco, vol. 5 March 1986, page 255, ref. 996,

and the further document

(22) A. Khojasteh et al., "Safety And Efficacy Of Slow-Release Morphine Sulfate Tablets In Cancer Pain Therapy": Proceed. of Asco, vol. 5 March 1986, page 256, ref. 1000,

codeine and morphine also showed a peak plasma level within the presently claimed range. There was no prejudice for a person skilled in the art against inferring the occurrence of the hydromorphone plasma level from corresponding results known from codeine or morphine. The claimed peak plasma level of hydromorphone obtained in vivo between 2 and 4 hours therefore constituted merely a discovery of inherent properties of hydromorphone formulations. Moreover, by using pharmacokinetic parameters known from additional prior art, namely document

(23) J. J. Vallner et al., "Pharmacokinetics and Bioavailability of Hydromorphone Following Intravenous and Oral Administration to Human Subjects, J. of Clin. Pharmacol. **21**, 152-156 (1981),

and document

(24) M. Gibaldi & D. Perrier, "Pharmacokinetics", page 33 to 39, Verlag Marcel Dekker Inc., New York 1975,

the skilled person even could have calculated the occurrence of the claimed peak plasma level of hydromorphone. In the light of two data sheets (25) and (26) forming annex to the grounds of appeal dated 7 April 1994, the Appellant explained how to carry out such calculations by using the technical information known from documents (23) and (24). There was no difficulty for a person skilled in the art to adjust any desired plasma peak of hydromorphone by controlling the dissolution rate of the dosage form. This was carried out in practice by applying well known galenical methods. Therefore, the alleged invention was not based on a surprising effect.

Moreover, having regard to a further data sheet (27), also forming an annex to the grounds of appeal, showing a graphical plot of data according to Example 1 of the patent in suit, it appeared that the plasma profile of hydromorphone did not only relate to a first order process but also comprised a zero order process over a period of 4 to 8 hours. On the basis of this finding the person skilled in the art expected a higher plasma level of hydromorphone after the occurrence of the peak plasma level.

The Appellant contended that even if there was evidence in the prior art for the preparation of a formulation having a peak plasma level of hydromorphone occurring after 4 to 8 hours, at a time outside the range according to claim 1 of the patent in suit, in the field of pain management there was in any case a strong motivation for a person skilled in the art to design a formulation which allows the relief of the patient's pain at a very early stage of the treatment.

Document (15) described metabolites of hydromorphone. Accordingly, the Respondent's argument that morphine and codeine underwent metabolism to powerful analgesics and therefore, the lack of such activity for hydromorphone rendered a comparison with these drugs pointless could not be maintained.

The Appellant furthermore alleged that the values of partition coefficients referred to by the Respondent for morphine and codeine on the one hand and hydromorphone on the other hand, were based on tests carried out in different solvent systems. It was therefore not permissible to conclude that there was in general a difference as to physical behaviour of these

drugs. This was proven by a further document (submitted at the oral proceedings) showing nearly the same values of partition coefficients for morphine and hydromorphone tested in the same solvent system.

V. The Respondent argued that document (12), although disclosing matrix formulations useful for the preparation of controlled release compositions, was not relevant when discussing obviousness of the subject-matter of the patent in suit. Apart from the fact that document (12) did not mention hydromorphone at all, it was well known and had been already considered by the Opposition Division that the *in vitro* release rate of an active ingredient did not always correlate with the expected *in vivo* pharmacokinetic profile or the expected pharmacological effects of said active ingredient.

Detailed studies about pharmacokinetics and pharmacodynamics of controlled release hydromorphone were unknown at the priority date of the patent in suit. By using all the information at that time available on immediate release hydromorphone, and by applying this information in the customary way, the skilled person came to the conclusion that in order to obtain analgesically effective plasma concentrations of hydromorphone over a 12 hour period, it was necessary to produce a formulation which gave the peak plasma level in the period of 4 to 8 hours. Accordingly, the skilled person did not inevitably arrive at the claimed formulation with a peak plasma level between 2 and 4 hours. This was proven by calculated and predicted plasma profiles from known and simulated parameter values of hydromorphone. The statutory declaration of Dr. Smith, attached to the letter dated 28 November 1994, related to such pharmacokinetic simulations and particularly showed that the data reported in document (23) confirm that a later peak plasma level

after 5.17 hours had been anticipated from a twelve-hourly controlled release formulation of hydromorphone. Calculations were based on a first order pharmacokinetic equation as known from document (24) and the values for immediate release hydromorphone from document (23). The Appellant had not provided any calculations of t_{max} for hydromorphone. Documents (25) and (26) merely comprised a reference to the theoretical background of pharmacokinetics and document (27) was based on data provided in Example 1 of the patent in suit. The use of such data not forming part of the prior art clearly was a matter of hindsight. Accordingly, the new documents (23) to (27) were not relevant for the assessment of inventive step.

At the oral proceedings, the Appellant no longer contested the overall results of the pharmacokinetic calculations presented in the statutory declaration of the Respondent's expert Mr. Smith, filed 28 November 1994.

Furthermore, the Respondent submitted that document (13) described the metabolism of morphine into a powerfully analgetic metabolite. Taking into account the lack of such activity for hydromorphone, as known from document (15), it was pointless to discuss obviousness of the subject-matter of the patent in suit in the light of known properties of morphine or codeine, which underwent metabolism to morphine. This was proven by declarations of experts. Moreover, in view of very different partition coefficients of hydromorphone on the one hand and morphine and codeine on the other hand, it was not possible to make firm predictions as to the absorption characteristics or analgesic properties of controlled release hydromorphone on the basis of those of morphine and/or codeine.

Documents (21) and (22) relating to morphine and codeine did not contain concrete information about the galenical formulation of the drugs. It was in any event misleading to talk about standard formulations suitable for each drug.

Taking into account plasma concentration profiles of commercially available controlled release morphine formulations, it was proven that the Appellant's submission that in the treatment of severe pain such as tumour pain an early onset of analgesic activity was always desirable, was not based on any evidence.

VI. The Appellant requested that the decision under appeal be set aside and that the European patent No. 0 271 193 be revoked.

The Respondent requested that the appeal be dismissed and that the patent be maintained.

Reasons for the Decision

1. The appeal is admissible.

2. The Board regards each of the new documents (21) to (27) filed by the Appellant as well as the statutory declarations filed by the Respondent at the appeal stage as an appropriate reaction to the Opposition Division's decision and being relevant when deciding on the question of inventive step in the present case. Accordingly, these documents are admitted into the procedure.

3. Neither of the prior art documents discloses the specific combination of dissolution rate *in vitro* and the occurrence of the peak plasma level of hydromorphone *in vivo* defined by product claim 1. The Board is thus satisfied that claim 1 relates to novel subject-matter (Article 54(1) EPC).

4. The relevant question in this appeal is whether or not the subject-matter of claim 1 of the patent in suit satisfies the requirements of Article 56 EPC in respect of inventive step.

4.1 The patent in suit relates to a solid oral dosage form comprising hydromorphone. The Board considers document (23) to be the closest state of the art, which describes oral administration of hydromorphone tablets. This was not disputed by the parties at the oral proceedings.

4.2 More particularly, document (23) relates to a so-called pilot study on the pharmacokinetics and absolute bioavailability of hydromorphone following crossover administration of tablets and injection to six male adult volunteers. The subjects received hydromorphone as 2 mg.ml intravenously and one 4 mg tablet orally on each of two study days separated by one week. Blood samples were withdrawn at 0, 15, 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 hours after oral administration. Hydromorphone levels in plasma were assayed by a modification of a morphine radio immunoassay procedure (see page 152/153 "Abstract" and "Materials and "Methods").

As a result of the study Table II on page 155 shows inter alia a mean absorption rate constant k_a = 2.355±2.231 (hr^{-1}) obtained after oral administration of the tablets. According to the explanations on page 155, left column, this absorption rate constant indicates a

half-life of absorption of about 18 minutes and predicts that maximum blood levels will be rapidly produced and absorption should be 90 per cent complete in about 1 hour. Additional support for the maximum plasma concentrations at 1 hour can be seen from the mean value of individual time of C_{max}=1.0±0.27 (hr) in Table III on page 155. It is pointed out on page 156, left column, last paragraph, that the 8- through 12-hour blood values are generally outside the limited scope of the standard curve and could only be estimated by taking a fourfold excess of plasma to stay within the range of the regression equation.

It was not disputed by the parties that 4mg hydromorphone tablets as used in the studies according to document (23) and marked under the trade name Dilaudid required in case of severe pain administration every 4 to 6 hours.

4.3 Starting from document (23) the problem to be solved is to provide a solid oral dosage form which affords therapeutic levels of hydromorphone *in vivo* over at least a 12 hour period, and may therefore be used on a twice daily basis (see also the originally filed application page 3, second paragraph and the patent specification page 2, lines 46 to 49).

4.3.1 The decision of the Opposition Division is based on the same problem but with reference to document (3), exclusively relating to morphine as the closest prior art. The formulation of the problem stated above under point 3.2, however, would clearly imply that a solid oral dosage form of **hydromorphone** was already known from this prior art. It is not the case. Accordingly, document (3) not relating to hydromorphone at all could in no way represent a proper starting point for the discussion of inventive step in the present case.

4.3.2 The problem defined under point 4.3 is solved by the solid controlled release oral dosage form according to claim 1 of the patent in suit. Having regard to the experimental evidence in the patent itself and the additional technical information contained in the statutory declarations attached to the Respondent's letter dated 28 November 1994, the Board is satisfied that the problem has indeed been solved. This was not disputed by the Appellant.

4.4 Document (23) itself does not contain technical information how to influence the pharmacokinetics and bioavailability of the orally administered 4 mg tablet dosage of hydromorphone and this document is wholly silent on a prolongation of the pharmacokinetic effect of hydromorphone. However, if there is a demand for a prolonged therapeutic activity of hydromorphone in accordance with the problem as stated above, the skilled person, aware of the fact that there is no other prior art available relating specifically to the problem of controlled released formulations of hydromorphone, inevitably will turn to prior art relating to controlled release formulations in general and, if available, of structurally similar analgesic active drugs.

4.5 Documents (3), (21) and (22) describe such controlled release formulations. The Board notes that in regard to this prior art the Appellant mainly has based its argumentation on the obviousness of the occurrence of the peak plasma level after administration of the drug.

Documents (3) and (22) relate to morphine, while document (21) deals with codeine.

4.5.1 The purpose of document (3) was to define more precisely the pharmacokinetic profile of sustained-release oral morphine sulphate tablets (MST Continus: Napp Laboratories), and the relationship between plasma morphine concentration and analgesia. Analgesia was assessed by determination of the so-called ischaemic tourniquet time (ITT). As a result it is inter alia summarized that the mean peak plasma morphine concentration occurred at a mean time of 142.5 min after ingestion and that a significant analgesic effect was still present at 420 min. There were differences in time relationship between mean plasma concentration and analgesia together with a lack of a direct correlation between ITT and plasma morphine concentration (see pages 821/822 "SUBJECTS AND METHODS", page 823 Figure 2 and page 826, left column third paragraph as well as the "SUMMARY" on page 821).

4.5.2 Document (22) also relates to oral slow-release morphine sulfate tablets, termed MS Contin (MSC), for the treatment of cancer pain. The bioavailability is compared to that of immediate-release morphine sulfate tablets (MSIR). MSC shows a maximum plasma concentration after 2.09±0.15 hrs whereas MSIR shows a maximum plasma concentration after 0.98±0.15 hrs. It is indicated that for most patients the dosing interval was lengthened to 12 h with a decrease in the total daily morphine requirement. It is pointed out that the MSC analgesia was judged to be better and side effects were equal to or fewer when compared with patients pre-study narcotics.

4.5.3 According to document (21), it is desirable to have controlled release formulations of other analgesics than morphine available in order to accommodate inter-patient differences. The bioavailability and pharmacokinetic characteristics of controlled release codeine (CRC) in comparison to immediate-release

codeine liquid (IRL) and tablet (IRT) is assessed. The peak plasma concentration of CRC occurred after 3.3 hours. It is indicated that the results are generally similar to those obtained in comparison of controlled and immediate-release morphine.

4.5.4 Documents (3), (21) and (22) themselves do not describe a formulation of the tablets.

4.6 Prima facie it might have appeared, in the light of this review on controlled release formulations of morphine and codeine which are known to have a chemical structure and some physico chemical parameters closely related to hydromorphone, that pharmacokinetic parameters of these compounds would be the obvious choice to achieve a prolongation of the pharmacokinetic effect of hydromorphone known from document (23).

4.6.1 However, when deciding on the question whether or not the skilled person would, in the light of the disclosure of pure pharmacokinetic parameters of the known analgesic controlled release formulations, have had an incentive to arrive at the solution of the problem underlying the patent in suit, all known developments at the priority date in the field of distribution, biotransformation and excretion of these drugs based on practical experience and clinical studies which appear to be relevant must be taken into consideration.

4.7 In this respect the Board is convinced that the skilled person would also have been aware of documents (13), (15) and the Board is satisfied that the statutory declaration attached to the letter dated 28 November 1994 (including a reference to the

statutory declaration attached to the letter dated 12 March 1993, on which the decision of the Opposition Division was based) represents the common general knowledge at the priority date.

4.7.1 According to document (13) (see particularly page 1549, right column under the paragraph "Discussion") and the said statutory declarations, it is clear that at the priority date of the patent in suit the skilled person was aware of the fact that morphine is converted *in vivo* into a significant amount of an active metabolite, morphine-6-glucuronide, which is itself a potent analgesic and that the prolonged duration of morphine is due, in part, to the formation of this active metabolite. It is finally pointed out in document (13) (see particularly page 1549, right column, last paragraph of "Discussion") that "...these studies" (-reference is made to previous studies of morphine pharmacokinetics-) "should be re-evaluated, with greater emphasis placed on the role of morphine-6-glucuronide in the clinical effects of morphine".

In this context it was furthermore known, that codeine also forms an active metabolite (morphine and its metabolites) which will contribute to its duration of action.

This was not contested by the Appellant.

4.7.2 Accordingly, when assessing the analgesic effect of morphine or codeine, it has to be accepted that some marked contribution to that effect is being afforded by the metabolite. As a consequence, when considering analgesia of these drugs over the long term it is not possible to disregard the individual serum levels of morphine and morphine-6-glucuronide. However, documents (3), (21) and (22) do not disclose such individual serum levels.

4.7.3 The situation with regard to hydromorphone was not so well established at the priority date of the patent in suit. Although it was known from document (15) (see page 1709, left column, preliminary remarks and formulas, and page 1712, right column, last paragraph) that some metabolites are produced *in vivo* after administration of hydromorphone, and a considerable amount of such metabolites which may have some pharmacological contribution can be found in guinea pig urine, it is clearly indicated that the relatively small amounts of metabolites found in rat, dog, rabbit, and human urine suggest that the contribution to pharmacological activity from the active metabolites would be minimal for these species.

4.8 In the light of the preceding paragraphs showing that a prolongation of the analgesic effect over 12 hours achieved by known controlled release formulations cannot be directly derived from the administered drug and that this prolongation results from a cumulative phenomenon, it is apparent that at the priority date of the patent in suit the skilled person was not in a position to predict or extrapolate the pharmacokinetics of a controlled release hydromorphone formulation based upon experimental data concerning morphine and/or codeine provided in documents (3), (21) and (22).

4.9 The Board agrees with the Appellant's view that it must be expected from the person skilled in the art faced with the problem of prolonging the analgesic activity of hydromorphone not only that he takes account of parameters relating to controlled release formulations known from the prior art and already put into practice, but also that he makes use of theoretical calculations known in the field of pharmacokinetics for the design of drug formulations.

4.9.1 Document (24) represents a well known textbook in the field of pharmacokinetics. According to chapter one of this book the so-called one-compartment model is the most commonly employed approach to the pharmacokinetic characterization of a drug. This model depicts the body as a single homogenous unit and is inter alia particularly useful for the pharmacokinetic analysis of plasma for drugs which rapidly distribute between plasma and other body fluids and tissues upon entry into the systemic circulation. On page 37 ff of this document it is shown how mathematical relationships can be developed to estimate the time at which a peak plasma concentration of drug should be observed and the maximum plasma concentration at this time following first-order input into the body.

There was also no dispute between the parties that at the priority date of the patent in suit it was possible for a pharmacokineticist, given basic data for a given active ingredient, to estimate the sort of plasma level profile that would be required to give an effective 12 hour therapeutic life and, accordingly, to estimate at what period the peak plasma level should (theoretically) be achieved.

4.9.2 Once the person skilled in the art has recognized that it is not promising to search in direction of a controlled release formulation of hydromorphone on the basis of the available data relating to controlled release **morphine** and/or **codeine**, the only way to continue search on the basis of theoretical calculations is to come back to data available on immediate release **hydromorphone** as described in document (23). The statutory declaration attached to the letter dated 28 November 1994 includes such theoretical calculations.

4.9.3 The undisputed overall results of these theoretical calculations based on one compartment models with first order absorption by using especially data from Table II of document (23) show a predicted mean value of 5.17 hours for the occurrence of the peak plasma level of hydromorphone after administration of the dosage form, a value outside the range of 2 to 4 hours required by claim 1 of the patent in suit.

Moreover, pharmacokinetic simulations contained in the said statutory declaration show in general that a skilled person would have expected to have to use a formulation giving a peak plasma level more than 4 hours after administration in order to achieve the desired 12 hour effect.

4.9.4 The Board agrees with the Appellant's point of view that documents (25) and (26) are suitable to demonstrate in a graphical way the above mentioned mathematical relationship based on pharmacokinetics for the so-called compartment models and, hence are suitable to demonstrating a theoretical way how to adjust any desired point of time t_{max} for the occurrence of the peak plasma concentration by manipulating the dissolution rate. These documents, however, do not contain any information as regards the preference of a so-called early or late occurrence of the t_{max} and do not contain any counter evidence as to the results of the statutory declaration. It was not contested by the Appellant that the data sheet (27) contains technical information disclosed for the first time in the patent in suit. Therefore, the Board can only conclude that any technical analysis based on the outcome of this document involves a discussion of the presently claimed subject-matter in an unfair way with knowledge of the invention.

4.9.5 Accordingly, there was, neither in the light of the available pharmacokinetic parameters derived from clinical studies based on analgesics already on the market, nor on the basis of simulated pharmacokinetic parameters using pure theoretical calculations, at the priority date of the patent in suit a clear teaching which might have lead one skilled in the art to the combination of parameters presently claimed.

4.10 It is also apparent from the foregoing that the mere fact that it was known before the priority date of the patent in suit how to adjust in practice any desired dissolution rate and peak plasma concentration by suitable galenics and auxiliaries, has no influence on the question under which circumstances a person skilled in the art **would** have chosen a specific combination of these parameters for hydromorphone. Therefore, the disclosure of document (12) relating in general to matrices for use in controlled release formulations without any preference for the parameter combination of the patent in suit, could neither alone, nor in combination with the other cited prior art, foreshadow the solution to the problem stated above.

4.11 The Appellant's final argument as to the obviousness *per se* of a so-called early t_{max} for the occurrence of the peak plasma concentration because of the fact that in the field of pain management there was in any case a strong motivation for a person skilled in the art to design a formulation which allows the reliefe of the patient's pain at a very early stage of the treatment, clearly is unconvincing. It is to be noted that the objective problem underlying the patent in suit was not

the provision of an immediate release oral dosage form, since pain relief at an early stage of the treatment with hydromorphone was already achieved by document (23).

5. The other prior art cited during the procedure has less relevance than the documents discussed above.

6. It is accordingly, the Boards view that the subject-matter of product claim 1 as well as dependent claims 2 to 10 for contracting states AT, BE, CH, DE, FR, GB, IT, NL and SE would not have been obvious from either citation taken singly or in combination. Thus, the required inventive step is not lacking and the said claims satisfy the requirements of Article 56 EPC.

7. The same reasoning applies to the subject-matter of process claims 1 to 10 for contracting state ES directed to the process for the preparation of the new and inventive solid controlled release oral dosage form as set out above.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. A. M. Lançon