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# D E C I S I O N
# of 20 July 2000

**Case Number:** T 0904/98 - 3.3.2

**Application Number:** 92912205.9

**Publication Number:** 0578780

**IPC:** A61K 31/60

**Language of the proceedings:** EN

**Title of invention:**
Suppression of thromboxane levels by percutaneous administration of aspirin

**Applicant:**
GUNDERSON MEDICAL FOUNDATION, LTD. et al

**Opponent:**
-

**Headword:**
Dermal Aspirin/GUNDERSON

**Relevant legal provisions:**
EPC Art. 52(1), 54, 56

**Keyword:**
"Novelty (yes)"
"Inventive step (yes); non-obvious solution; finding that dermal aspirin does not affect prostaglandin levels, while effectively suppressing thromboxane levels in a mammalian subject, not a mere "bonus effect", but achievement of a desirable therapeutic goal in its own right"

**Decisions cited:**
G 0005/83

**Catchword:**

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Beschwerdekammern | Boards of Appeal | Chambres de recours

**Case Number:** T 0904/98 - 3.3.2

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.2**
**of 20 July 2000**

**Appellant:** GUNDERSON MEDICAL FOUNDATION, LTD. et al
1836 South Avenue
LaCrosse, WI 54601 (US)

**Representative:** Brown, John David
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**Decision under appeal:** **Decision of the Examining Division of the European Patent Office posted 23 April 1998 refusing European patent application No. 92 912 205.9 pursuant to Article 97(1) EPC.**

**Composition of the Board:**

**Chairman:** P. A. M. Lançon
**Members:** G. F. E. Rampold
C. Rennie-Smith

## Summary of Facts and Submissions

I. European patent application No. 92 912 205.9, published as WO 92/20 343, was refused under Article 97(1) EPC by a decision of the examining division posted on 23 April 1998. The decision was based on claims 1 to 16 filed during oral proceedings held on 13 March 1997. Claim 1 was worded as follows:

*"Use of aspirin for the manufacture of a pharmaceutical preparation for suppressing thromboxane levels in a mammalian subject without affecting prostacyclin levels or resulting in gastrointestinal toxicity, the pharmaceutical preparation comprising aspirin and a support for maintaining said aspirin in a form for percutaneous absorption by said skin, wherein said aspirin is present in an amount sufficient to reduce thromboxane levels in said subject by more than 50%."*

Dependent claims 2 to 16 related to specific elaborations of the use according to claim 1.

II. In the course of the proceedings before the examining division reference was made, inter alia, to the following documents:

(1) Naito et al. "Percutaneous Absorption of Salicylic Acid Derivatives" published in Japanese Pharmacology & Therapeutics, vol. 16, no. 1, 1988, pages 17 to 25

(3) FR-A 2 295 753

(4) J. Hirsh et al. "Aspirin and Other Platelet Active Drugs" published in Chest, vol. 95, no. 2, 1989, pages 12S to 18S)

(5) WO 91/00096

III. The stated ground for the refusal was that the invention did not involve an inventive step, having regard to the disclosure in citation (5), and in particular also in citation (1). The substance of the reasoning given in the decision of the examining division was as follows:

The present application and the closest state of the art, which was citation (5), sought to solve essentially the same problem, this problem being the suppression of thromboxane levels and platelet aggregation in the human blood system by the administration of aspirin via a non-oral route, in order to avoid adverse side effects such as gastrointestinal disorders. In the state of the art according to (5) it was proposed to solve this problem by the administration of aspirin in the form of a sublingual lozenge.

Since, in the opinion of the examining division, citation (1) suggested to a person skilled in the art that the percutaneous administration of aspirin according to present claim 1 was a promising alternative to the sublingual administration disclosed in (5), the proposed solution of the above-identified problem was considered to be the result of an obvious combination of the teachings of citations (1) and (5).

IV. The appellant (applicant) lodged an appeal against this decision. The statement of grounds was accompanied by two declarations of the joint inventors of the present application, Mr Rudolph M. Keimowitz and Mr Desmond J. Fitzgerald.

V. At the beginning of the oral proceedings, held on 20 July 2000, the appellant submitted in substitution for all previously filed requests a revised set of claims forming the sole remaining request. Claims 1 to 15 of this request correspond to claims 1 to 10 and 12 to 16 filed on 13 March 1997 during the oral proceedings before the examining division (see paragraph I *supra*).

VI. The appellant's submissions presented in writing and during oral proceedings can be summarised as follows:

Since with sublingual administration of aspirin, as disclosed in citation (5), the dosage was primarily received when the patient swallowed saliva containing the dissolved drug, the cited document failed, contrary to the assertion of the examining division, to teach administering aspirin to the blood plasma by a non-oral route. In both oral and sub-lingual administration, the drug was released into the bloodstream only after its contact with the gastrointestinal tract. Thus, (5) provided no evidence that gastric disturbance was avoided or effectively reduced by sublingual aspirin dosage.

Citation (1) did disclose percutaneous administration of aspirin, but provided no teaching or suggestion as to potential uses of such dermal aspirin, much less whether percutaneous administration was even feasible

or desirable for lowering thromboxane levels. By comparison, citation (3) pertained to percutaneous administration of aspirin, but with treatment solely directed to analgesic effects.

The mode of action of aspirin for effecting analgesia was very different from that for lowering thromboxane levels. Whereas an effective antithrombotic therapy required the release of sufficient quantities of aspirin in its intact, acetylated form into the bloodstream, an acetyl group was not necessary when aspirin was used for the treatment of analgesia.

In fact, aspirin was known to be very unstable, having a short biological half-life in systemic circulation and being quickly hydrolyzed to salicylic acid in the gastrointestinal tract. Contrary to the finding of the examining division, citation (1) in no way taught that intact aspirin reached the bloodstream after percutaneous administration. In particular, the authors of (1) never measured the quantities of intact acetyl salicylic acid in blood plasma. What they actually measured in (1) were the quantities of the drug as salicylic acid following oral or dermal administration of aspirin.

The features "without substantially affecting prostacyclin levels or resulting in gastrointestinal toxicity" were not merely "bonus effects" but were part of the problem that was addressed and solved by the appellant’s invention. In view of the known instability of acetyl salicylic acid it was unexpected that dermal aspirin could be absorbed through the skin in its intact acetylated form in sufficient quantities and with sufficient stability to lower thromboxane levels

by more than 50% without substantially affecting prostacyclin levels or resulting in gastrointestinal disorders.

VII. The appellant requests that the decision under appeal be set aside and a patent be granted on the basis of the "Main Request" (being the only request) filed during the oral proceedings.

## Reasons for the Decision

1. The appeal is admissible.

2. Claims 1 to 17 as originally filed were directed to a method for inducing thromboxane suppression by percutaneously administering aspirin (acetyl salicylic acid) to a mammalian subject. Since such claims would fall under the prohibition of Article 52(4) EPC, during the proceedings before the examining division, all claims were drafted in the form for the protection of the "second or further medical indication" of a medicament, according to decision G 5/83 (OJ EPO, 1985, 64).

2.1 All references below to support for the present version of the claims in the application as filed are to the international application as published under the PCT (WO 92/20343). In particular:

the feature being additionally included in claim 1 "sufficient to reduce thromboxane levels by **more than 50%**" is taken from page 6, lines 3 to 4;

the feature **"without affecting prostacyclin levels"** finds its support in claim 12 as originally filed in conjunction with the disclosure in the paragraph bridging pages 6 and 7 and Example 3;

the feature **"without resulting in gastrointestinal toxicity"** finds its counterpart on page 5, lines 8 to 9; dependent claim 2 is based on the embodiments described on page 5, lines 17 to 20 and dependent claim 13 on those described on page 3, line 23;

dependent claims 3 to 12, 14 and 15 are based on the original ones in the following order:

- present claims: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 15

- original claims: 5, 3, 4, 8, 9, 10, 11, 13, 14, 16, 6, 7.

2.2 All claims are therefore acceptable as being supported by the disclosure of the application as filed and complying in this formal respect with Articles 84 and 123(2) EPC.

3. The invention relates to the use of aspirin in a galenic formulation suitable for percutaneous administration (hereinafter referred to as **"dermal aspirin"**) as a medicament for reducing thromboxane levels in a mammalian subject by more than 50% without simultaneously affecting prostacyclin levels or causing gastrointestinal disorders. The medicament is thereby applied topically to a patient's skin such that aspirin is percutaneously absorbed into the blood stream to achieve the desired therapeutic effect. The galenic

formulation of the medicament used for this treatment comprises a support or carrier which is conventionally used for the application of topical agents, preferably propylene glycol, and which contains the aspirin in a solubilized form, optionally along with other active agents and pharmaceutically acceptable adjuvants. The medicament preferably used in the present application contains approximately 9% aspirin (see page 5, lines 17 to 30; page 10, lines 15 to 21; claims 1 to 3).

3.1 Having regard to the state of the art known from the documents available in the proceedings, it has to be decided, in the board's judgement, whether citation (5), relied on by the examining division in the decision under appeal as the closest state of the art, or citation (3), cited in the search report and referred to as relevant state of the art in the official communications of the examining division of 11 November 1996 and 30 June 1997, comes closer to the claimed subject-matter of the application.

3.2 Citation (5) seeks to overcome certain well known problems arising from the deacetylation of aspirin in the gastrointestinal tract (ie conversion of acetyl salicylic acid to salicylic acid) to a variable but significant extent in different individuals following its oral administration. The major problems addressed in (5) concern in general the increased tendency of deacetylated or partially deacetylated aspirin to cause gastrointestinal disorders, stomach irritation, ulcers, etc. and, more specifically, its reduced capability or even incapability effectively to suppress thromboxane levels and control platelet aggregation in the human blood system (see especially page 1, penultimate paragraph to page 3, line 11).

Although the problems mentioned above have clearly been recognised in (5) as being primarily caused by oral administration of aspirin, the solution offered in (5) was simply the provision of a **tablet** containing a relatively small amount of aspirin capable of rapid dissolution or disintegration in the **oral**, preferably sublingual, cavity. The board concurs with the statement in Mr. Keimowitz' declaration to the effect that, with sublingual administration of aspirin as disclosed in citation (5), the dosage is primarily received when the patient swallows saliva containing the dissolved drug and that accordingly (5) provided no evidence as to whether gastric disturbance is effectively reduced by sublingual aspirin dosage which is in fact merely a specific galenic formulation of **oral aspirin**.

3.3 On the other hand citation (3) does actually pertain to the use of **dermal aspirin** as an advantageous **alternative to oral dosage forms of aspirin** for certain therapeutic applications. The medicament disclosed in (3) comprises aspirin in an amount of 1 to 25% by weight solubilized in a liquid or glutinous carrier or support which is selected from those conventionally used for the application of topical agents, for example, different sorts of hydrogenated vegetable fats or polyoxyethylene glycols.

Hence, comparison of the invention, as outlined in point 3 *supra*, with the prior art of (3), establishes that the medicament used in (3) does not differ from that in the present application with regard to

- the active agent of the medicament,

- the medicament's galenic formulation,

- the mode of its administration and

- the benefits arising from the dermal aspirin bypassing the gastrointestinal tract, thereby eliminating or at least reducing the risk of gastrointestinal side effects, including bleeding.

The sole difference consists in the proposed intended therapeutic application of the medicament. According to (3), dermal aspirin has an indisputable quality as an anti-inflammatory or analgesic agent and can be used to treat all sorts of localized pains normally requiring a local treatment, such as rheumatism, arthritis, traumatism, stiffness and contusions as well as in the treatment of burns, such as sunburns, rushes, insect stings, small wounds, etc (see (3): page 3, lines 20 to 31).

3.4 In view of the foregoing considerations, the board reaches the conclusion that the disclosure of (3), relating to **dermal aspirin** as a medicament in a suitable galenic form for various therapeutic applications, comes closer to the subject-matter of the invention than the disclosure of any other cited document, including citation (5), which essentially teaches an improved method of **oral administration of aspirin**. Taking into account that the sole difference between the prior art of (3) and the claimed invention resides in the different therapeutic application of the same medicament and, moreover, that the claims, as they now stand, are directed to the protection of a "second or further therapeutic application" of dermal aspirin, the prior art of (3) is considered to be the most

promising starting point to arrive at the claimed subject-matter in the application.

4. Thus, starting from citation (3) as the closest state of the art, **the problem** to be solved by the present application consists in providing a further therapeutic use or application for dermal aspirin.

According to claim 1 it is suggested to **solve this problem** by using **dermal aspirin** as an antithrombotic agent to suppress thromboxane levels in a mammalian subject by more than 50% without simultaneously affecting prostacyclin levels or causing gastrointestinal toxicity.

4.1 The thromboxane level in a mammalian subject is a significant and important physiological parameter that is exactly and easily measurable and recordable by standard diagnostic methods and is indicative of an individual's physiological and clinical risk in cardiovascular and cerebrovascular diseases such as myocardial infarction and stroke [see eg citations (4) and (5)]. Its reduction by more than 50% in a mammalian subject, as required by claim 1, is therefore **a precisely defined therapeutic application of dermal aspirin** within the meaning of Article 52(4) EPC for the purpose of treating and preventing various diseases benefiting from suppression of thromboxane levels, for example, cerebrovascular and cardiovascular diseases such as ischemic heart disease.

5. After examination of the documents uncovered by the search report and of those introduced during the examination and appeal procedures, the board is satisfied that none of them discloses the specific

therapeutic application of dermal aspirin mentioned-above. The subject-matter of the claims is accordingly deemed to be novel within the meaning of Article 54(1) EPC on the basis of the principles set out in decision G 5/83 (*loc. cit.)*. Since the board concurs with the opinion of the examining division in this point, there is no need for further detailed consideration of this issue.

6. The question arises whether the problem defined above has indeed been solved in all its different aspects by the features recited in Claim 1.

6.1 It can be derived from the tabulated test results in Table 1 on page 11 and likewise from Figures 1 and 2 of the specification that five successive daily applications of **dermal aspirin** in accordance with the application caused in all five subjects tested a decrease in thromboxane levels of at least 50%. The two subjects that continued therapy in accordance with the application for another five days had further marked reduction in thromboxane levels by Day 10 of 95 and 97%.

6.2 Further, from Figure 3 in conjunction with the disclosure in the paragraph bridging pages 6 and 7 of the specification, it can be seen that application of the highest dosage unit of 750 mg/day of **dermal aspirin** caused, based on urinary PGI-M determinations as an index of *in vivo* $PGI_2$ biosynthesis, only a small decrease in the prostaglandin ($PGI_2$) level due to a small fall in $PGI_2$ biosynthesis by day 4, while no further reduction occurred despite continued application, and by day 10 the level remained at 83% of baseline. This finding is confirmed by the tabulated

test results in Table 2 on page 15 of the specification, which show that, despite the evidence of marked decrease of thromboxane levels (see TX-M pre-ASA *vs.* TX-M post-ASA), there was no statistically significant change in basal prostacyclin ($PGI_2$) levels (see PGI-M (rest) pre-ASA *vs.* PGI-M (rest) post-ASA).

Moreover, the data in Table 2 show that $PGI_2$ formation in response to bradykinin infusion was substantially unaltered following **dermal aspirin** administration at a dose of 750 mg/day. This provides evidence that dermal aspirin did not substantially affect prostacyclin ($PGI_2$) levels (see PGI-M (stim) pre-ASA *vs.* PGI-M (stim) post-ASA).

In contrast, as can be seen from the comparative data in Table 2, 75mg/day of **oral aspirin** markedly suppressed both basal (see PGI-M (rest) pre-ASA *vs.* PGI-M (rest) post-ASA) and bradykinin-stimulated PGI-M excretion (see PGI-M (stim) pre-ASA *vs.* PGI-M (stim) post-ASA). This provides evidence of a substantial reduction in prostaglandin ($PGI_2$) levels following **oral administration of aspirin.**

6.3 According to the disclosure on page 12, lines 8 to 10, all hemocults taken from the 5 subjects tested were negative and no gastrointestinal symptoms or other side effects were noted or reported by them.

6.4 Consequently, in view of the results obtained in the examples of the present application and in the absence of any evidence to the contrary, the board is satisfied that the problem in all its different aspects, as defined above, is plausibly solved.

7. It remains to be examined whether, in view of the technical problem to be solved, the requirement of inventive step is met by the claimed use.

7.1 The board concurs with the appellant's submission during oral proceedings that the comparative results shown in citation (1) regarding delivery of **dermal aspirin** and salicylic acid (see especially Figure 3 (B), 4 (B), 6 and the corresponding text in the paragraph bridging pages 23 and 24) could not result from intact aspirin reaching the bloodstream, but rather from different degrees of retention of aspirin and salicylic acid in the various ointments tested. As indicated at the end of page 23 of (1), the comparative results refer to the level of **cutaneous absorption** of aspirin and salicylic from the different ointments used.

Contrary to the view of the examining division in the decision under appeal, the board cannot find in citation (1) any teaching or suggestion to the effect that **intact aspirin** would in fact be capable of reaching the bloodstream following percutaneous absorption. Nowhere is there evidence in (1) that blood plasma levels of **intact aspirin** have been measured. Further, since the cited document does not refer to any potential use or therapeutic application of such **dermal aspirin**, the disclosure of (1) is not considered to be relevant to the assessment of inventive step in the present case.

7.2 Although at the publication date (December 1974) of citation (3) at least some evidence was already available to a person skilled in the art that aspirin might be effective as an antithrombotic agent in

patients with cerebrovascular disease and ischemic heart disease [see eg (4): references 19, 57, 61, 62], the disclosure of (3) is entirely silent as to any possible antithrombotic effect of **dermal aspirin** or its potential use to suppress thromboxane levels or control platelet aggregation in the human blood system.

At the priority date, however, aspirin had become widely used as an antithrombotic agent to treat a broad spectrum of medical conditions benefiting from suppression of thromboxane levels. The skilled person also knew that aspirin causes the lowering of thromboxane levels by irreversibly acetylating the enzyme cyclooxygenase. Thus the acetyl group of aspirin, while not required to exhibit its analgesic effect, is necessary for lowering thromboxane levels, as is described, for example, in documents (4) and (5).

7.3 The skilled person with this knowledge seeking to solve the technical problem, would certainly have noticed that the detection of the presence of acetyl salicylic acid (aspirin) in the urine following the administration of **dermal aspirin** was taken in (3) as an evidence that acetyl salicylic acid was capable of passing the skin barrier (see especially page 4, lines 20 to 24).

The question that arises is whether the skilled person would have arrived at the claimed solution of the stated problem by considering the above-mentioned disclosure in citation (3). In answering this question the board notes that the presence of intact aspirin in the bloodstream is not described and cannot, at least not explicitly, be derived from the disclosure of (3), much less whether percutaneous administration would

even be feasible or desirable for lowering thromboxane levels. In this respect it must also be kept in mind that acetyl salicylic acid was applied in (3) for analgesia (pain relief) only, for which an acetyl group is not necessary to achieve the desired therapeutic effect. The information given in (3) must, moreover, be considered in the context of the skilled person's general knowledge at the priority date that the ester linkage between the acetyl group and the salicylic acid molecule is easily broken and that the absorbed aspirin is readily metabolized to the largely inactive salicylate by esterases present in the skin tissue and physiological fluids, such as blood and water, before it reaches systemic vasculature.

In the light of the considerations set out above, the board concludes that the actual information derivable from (3) must be considered too vague and general to point the skilled person positively in the direction of the claimed invention. Even if he had conceivably learned from (3) the basic capability of dermal aspirin to pass the skin barrier in an entirely unspecified amount or concentration, the disclosure of (3) fails to provide any useful suggestion whatsoever as to the quantities of acetyl salicylic acid effectively absorbed into the bloodstream through the skin, let alone as to whether such quantities would be sufficient to reduce thromboxane levels by more than 50% as required in claim 1.

7.4 Moreover, the adequate solution to the stated problem not only requires the reduction of thromboxane levels by more than 50% but also their **selective reduction** without simultaneously affecting to any significant extent vascular prostacyclin activity and, accordingly,

the patient's prostacyclin ($PGI_2$) level.

Apart from the fact that the desirability as a therapeutic goal **of improving the selective effect of a medicament** is commonly acknowledged in the art, at the priority date it was known to a person skilled in the art that the **desired** inhibition of thromboxane $A_2$ ($TXA_2$) synthesis caused by aspirin is accompanied by the **undesired side-effect** of inhibition of endothelial prostacyclin ($PGI_2$) activity. $PGI_2$ is the major cyclooxygenase product of vascular endothelium and is a potent platelet inhibitor. As such, it plays a major role in regulating platelet activity and thromboxane levels in vivo. Consequently, the capability of aspirin to suppress thromboxane levels and its antiplatelet and antithrombotic effects may be attenuated by coincident inhibition of vascular prostacyclin activity and consequential reduction of prostacyclin ($PGI_2$) levels (see eg (4), page 12S to page 13S, right hand column, end of the 2nd full paragraph, especially page 13S, left hand column, lines 13 to 27).

As can be derived from the comparative data in Table 2 of the present application and likewise from the disclosure in (4), it does not appear possible to achieve selective suppression of thromboxane levels with chronic administration of standard oral aspirin. In this respect it is noted that certain data provided in (4) suggest that **oral aspirin** is about as equally effective as an antithrombotic agent at doses at which prostaglandins are inhibited. These two different effects of oral aspirin do not appear to have necessarily been dependent on the administration of high dosage rates. The same effects were similarly observed, when aspirin was administered at doses as low

as 35 mg/day for 7 days which are desirable for suppressing thromboxane levels (see especially page 13S, left hand column, end of the first full paragraph).

7.5 Thus, on the basis of the evidence available in the proceedings, the board is satisfied that, at the priority date, the **low selective effect** of **oral aspirin** in the suppression of thromboxane levels was recognised as being a problem from a therapeutic point of view for which the state of the art did not offer a satisfactory solution.

In view of the foregoing, the finding that dermal aspirin does not affect in any significant way prostaglandin levels, despite its capability of reducing the thromboxane levels by more than 90% (see eg Tables 1 and 2, Figures 1 and 2), cannot be seen merely as an extra effect obtained by way of a bonus in the context of solving the problem of suppressing thromboxane levels. It amounts rather to the achievement of a desirable therapeutic goal in its own right, particularly since many of the clinical conditions in which aspirin is used as an effective antithrombotic agent require the drug to be used over a long term or even indefinitely (see (4), especially page 12S, middle of right hand column). As mentioned above, at the priority date of the present application, this desideratum had not then, *prima facie*, actually been achieved.

7.6 In summary, the board reaches the conclusion that the complete solution of the stated problem cannot be inferred in an obvious manner from any of the citations available in the proceedings, since none of them would

lead the skilled person to consider using dermal aspirin for the effective and selective suppression of thromboxane levels in a mammalian subject without simultaneously affecting prostacyclin levels. The non-obviousness of the use of dermal aspirin according to claim 1 also imparts an inventive step to the subject-matter of each of dependent claims 2 to 15 relating to specific elaborations of the use according to the independent claim.

## Order

## For these reasons it is decided that:

1. The decision of the Examining Division is set aside.

2. The case is remitted to the department of the first instance with the order that a patent be granted on the basis of claims 1 to 15 of the "Main Request" filed during oral proceedings and a description to be adapted thereto.

The Registrar: The Chairman:

M. Dainese P. A. M. Lançon