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 23 January 1997

Case Number: T 1057/92 - 3.3.4

Application Number: 89902136.9

Publication Number: 0082182

IPC: A61K 35/14

Language of the proceedings: EN

Title of invention:
Composition based on the hemostatic agent factor VIIa and method of preparing same

Patentee:
BAXTER INTERNATIONAL INC.

Opponent:
(01) Novo Industri A/S
(02) Stichting Centraal Laboratorium van de Bloedtransfusiedienst van het Nederlandse Rode Kruis

Headword:
Factor VIIa/BAXTER

Relevant legal provisions:
EPC Art. 54, 56

Keyword:
"Prior use made publicly available (no)"
"Novelty (yes)"
"Inventive step (yes)"

Decisions cited:
-

Catchword:

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 1057/92 - 3.3.4

D E C I S I O N
of the Technical Board of Appeal 3.3.4
of 23 January 1997

Appellant: (Opponent 02)
Stichting Centraal Laboratorium van
de Bloedtransfusiedienst van het Nederlandse
Rode Kruis
Plesmanlaan 125
NL-1006 AD Amsterdam (NL)

Representative:
Wiegerink, Franciscus Johannes
Nederlandsch Octrooibureau
Scheveningseweg 82
P.O. Box 29720
2502 LS 's-Gravenhage (NL)

Respondent: (Proprietor of the patent)
BAXTER INTERNATIONAL INC.
One Baxter Parkway
Deerfield, IL 60015 (US)

Representative:
Bassett, Richard Simon
ERIC POTTER & CLARKSON
St. Mary's Court
St. Mary's Gate
Nottingham NG1 1LE (GB)

Other party: (Opponent 01)
Novo Industri A/S
Novo Allé
DK-2880 Bagsvaerd (DK)

Representative:
Brown, John David
FORRESTER & BOEHMERT
Franz-Joseph-Strasse 38
80801 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 24 March 1992 rejecting the opposition filed against European patent No. 0 0821 182 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairwoman: U. M. Kinkeldey
Members: R. E. Gramaglia
S. C. Perryman
L. Galligani
W. Moser

Summary of Facts and Submissions

I. European patent No. 0 082 182 having application No. 82 902 136.9 and claiming the priority date of 25 June 1981, was granted to the Respondent on the basis of claims 1 to 15. Claim 1 read as follows:

"1. A therapeutic composition of factor VIIa, which is sterile and in which factor VIIa is the sole effective activated hemostatic agent, for use in counteracting deficiencies of blood clotting factors or the effects of inhibitors to blood clotting factors in a patient."

Claims 2 to 8 were directed to special embodiments of claim 1. Claim 9 was in the form of a second medical use of factor VIIa. Claims 10 and 11 related to a vial comprising dry factor VIIa, while claims 12 to 15 were directed to a method for making the therapeutic composition according to claim 1.

II. Oppositions were filed by the Appellant (Opponent (O2)) and the Other Party (Opponent (O1)) on the grounds of Articles 100(a) and 100(b) EPC, ie lack of novelty, lack of inventive step and insufficiency of disclosure having regard in particular to the oral disclosure made by Dr Ulla Hedner during the International Meeting on Activated Prothrombin Complex Concentrates (APCCs) held in Rome on 30 and 31 March 1981 (document (D3)).

III. During the oral proceedings before the Opposition Division held on 21 January 1992 evidence was taken by hearing the witnesses Dr Hedner, employed by the Other Party, Dr Over, employed by the Appellant and Dr De Vrecker, employed by the Respondent, which witnesses had all attended the meeting in Rome on 30 and 31 March 1981.

IV. The oppositions were rejected pursuant to Article 102(2) EPC by the decision of the Opposition Division given orally on 21 January 1992, with the written decision notified to the parties being dated 24 March 1992.

V. The Appellant filed a notice of appeal against this decision, duly paid the appeal fee and filed a Statement of Grounds of Appeal.

The Other Party also filed a notice of appeal against this decision, duly paid the appeal fee and filed a Statement of Grounds of Appeal and further evidence, but withdrew the appeal by letter dated 21 October 1996.

The Respondent filed counterarguments.

The following documents are referred to in the present decision (the respondents' numeration suggested in the submission of 23 June 1993 has been adopted):

(A10) Kisiel et al., Thromb. Res. Vol. 22, pages 375-380 (1981)

(A18) Affidavit of Dr Hedner dated 7 September 1992

(A21) Stead et al., J. Biol. Chem. Vol. 251, pages 6481-6488 (1976)

(A24) Fujimaki et al., The Second International Symposium on Hemophilia Treatment, Program and Abstract, page 39, (Tokyo, March 13 and 14, 1981)

(A25) Østerud et al., Thrombos. Haemostas., Vol. 35, pages 295-304 (1976)

(A26) Fujimaki et al., Proceedings of the 2nd International Symposium on Hemophilia Treatment, pages 223-229 (1981)

(A27) Hutt et al., Journal of Laboratory and Clinical Medicine, Vol. 79, pages 1027-1034 (1972)

(A28) Hougie et al., "Blood Coagulation and Haemostasis" edited by J.M. Thomson, Churchill Livingstone, Chapter 1, pages 1-23 (1980)

(D3) Oral presentation made by Dr Hedner at the International Meeting on Activated Prothrombin Complex Concentrates "The State of the Art in Managing Hemophilia in Patients with Factor VIII Inhibitors" held in Rome on 30 and 31 March 1981.

(D4) Kurczynski et al., The New England Journal of Medicine, Vol. 291, pages 164-167 (1974)

(D6) Seligsohn et al., Blood Vol. 53, pages 828-837 (1979)

(D7) Hultin et al., Blood Vol. 54, pages 1028-1038 (1979)

(D8) Ofusu et al., Thromb. Res., Vol. 21, pages 23-33 (1981)

(D9) Activated Prothrombin Complex Concentrates, edited by G. Mariani, M.A. Russo and F. Mandelli, Preager Ed. New York, pages 73-126 (1982)

(D11) Hedner et al., J. Clin. Invest., Vol. 71, pages 1836-1841 (1983)

(D12) Hyland/Travenol "*Autoplex*" (1979)

(D13) Penner at al., Sem. Thromb. Hemostasis 1, pages 386-399 (1975)

(D15) Aronson et al., Hemophilia and Hemostasis, Alan Liss New York, pages 103-121 (1981)

(UH4) Clinical report of Dr Hedner dated 7 September 1992.

VI. In a communication 27 June 1996 accompanying the summons to oral proceedings, the Board stated the issues to be discussed. The Appellant and Other Party indicated that they would not attend the oral proceedings. These were held on 23 January 1997 in the absence of the Appellant and the Other Party.

VII. The Appellant's submissions can be summarized as follows:

Novelty (Article 54 EPC)

- The composition of claim 1 was anticipated by oral presentation by Dr Hedner to a Rome Symposium (Document (D3)) in March 1981. Dr Hedner reported that she administered purified Factor VIIa preparation, ie, a composition falling within the terms of claim 1 of the patent in suit, to two dogs and announced that she would in the near future test pure factor VIIa in haemophilia patients in association with a bleeding episode. In the appellant's opinion, making serious plans for a certain use that has been disclosed to the public anticipates that use.

- In her presentation at the Rome Symposium, Dr Hedner said that her factor VIIa preparation contained traces of factor XIIa used for activating factor VII to factor VIIa. However,

document (A21) showed that factor XIIa could not act as a blood clotting factor because the antithrombin-heparin cofactor, present in blood, acted as an inhibitor of factor XIIa activity and did so instantaneously, so factor XIIa could not be defined as a clotting factor in the sense of claim 1. The fact that factor XIIa in Dr Hedner's factor VIIa preparation was of no significance was also confirmed by the results of Dr Hedner's clinical tests showing no increase in the factor XIIa amount after infusion of her preparation (see clinical protocol (UH4)), as well as by Table II on page 1839 of document (D11). Moreover, even assuming, by way of hypothesis, that factor XIIa were a clotting factor, it would not be necessary to remove or inhibit the factor XIIa because there was not enough to have any activity *in vivo*. Taking into account that claim 1 did not exclude the presence of other activated blood clotting factors, provided that the composition gave no detectable haemostatic effect if the factor VIIa activity was inhibited or, after the separation of the factor VIIa, the residual components had no such effect (column 3, lines 19-28 of the patent in suit), the factor VIIa composition Dr Hedner intended to use satisfied the requirement recited in claim 1 that factor VIIa should be the sole effective activated haemostatic agent.

- In any event method claims 12 to 15 did not require the removal of any activated haemostatic agent which is not factor VIIa, so that for these claims absence of any other activated haemostatic agent could not establish novelty over the disclosure at the Rome Symposium.

- Further the Opposition Division had been wrong not to allow into the proceedings further evidence sought to be introduced at the oral proceedings before the Opposition Division relating to two haemophiliac patients who were treated with pure factor VIIa in Sweden by Dr Hedner for controlling bleeding before the priority date of the patent (see Affidavit (A18) and exhibit (UH4), a clinical report which had been included as Table II in Dr Hedner's later publication (D11)). The evidence showed that this information was made available to the public and destroyed the novelty of the claims.

Inventive step (Article 56 EPC)

- To the skilled person aware of the powerful haemostatic properties of factor VII (known since 1956) and of the concept of the blood coagulation cascade (suggested in 1964), elevation of factor VII above physiological levels by adding factor VII would have been an obvious step to increase the haemostatic potential of the factor VIIa-dependent pathway (i.e, the extrinsic pathway, see point 19 infra) *in vivo*. Already in 1974, document (D4) (see page 166, r-h column, lines 22 to 23) suggested that large quantities of factor VII were present in the APCCs accelerated coagulation process through the extrinsic system.

- The claims were obvious because, before the priority date of the patent in suit, there was a clear and unambiguous signal (see eg., documents (D6), (D8), (A24) and (A25)) to those skilled in the art that it was worth investigating the extent to which Factor VIIa alone was effective in counteracting deficiencies of blood clotting

factors or the effects of inhibitors to blood clotting factors in haemophilia patients.

- The authors of document (D6) made the hypothesis that factor VIIa was the by-passing agent looked for. However, they could not test this experimentally because no purified factor VIIa was available to them.

- Document (D8) pointed out that a potential pathway for by-passing factor VIII in haemophilic plasma was the activation of factor X by factor VIIa, which itself resulted from by activation of factor VII by factor IXa. Thus there were only two possibilities to be tried, namely factor VIIa and factor IXa.

- Efforts to identify the active component in APCC focused on three candidates only, namely factor Xa, factor IXa and factor VIIa. Factor IXa was known to activate factor X to factor Xa in a factor VIII-dependent fashion (see preceding paragraph) and factor VIII was missing in patients treated with APCCs. Thus, factor IXa could not be the by-passing agent. Further, according to document (A25), antithrombin III present in blood turned out to inhibit both factor IXa and factor Xa, but not factor VIIa. Thus, factor IXa and factor Xa were poor candidates as by-passing agents and everyone suspected that factor VIIa was the by-passing agent looked for and could be used as the sole haemostatic agent, but nobody could test this hypothesis until purified human Factor VII was available.

- It was in this context that Dr Hedner made an oral presentation to the Rome Symposium (document (D3)), in connection with the treatment of

haemophilia patients. Dr Hedner reported that she obtained purified Factor VIIa and had administered 50 or 100 µg/kg of this preparation to two dogs. She had found that purified Factor VIIa did not induce any change in the coagulation or fibrinolytic system and no thrombogenic side effects were noticed. Dr Hedner was so sure of success that she also announced that she would in the near future test pure factor VIIa in haemophilia patients in association with a bleeding episode. Dr Hedner's approach based on the administration to dogs of a factor VIIa preparation was an indication that everybody acknowledged factor VIIa as the most likely candidate for being the by-passing agent looked for.

VIII. The Respondent submitted essentially the following arguments:

Novelty (Article 54 EPC)

- The prior use on patients in Sweden has not been proven to be public.

- The Appellant, who had the burden of proof, did not provide evidence that factor XIIa in Dr Hedner's preparation would not have a haemostatic effect. Factor XIIa was indeed a blood clotting factor (document (A28)). Contrary to the arguments of the appellant, factor XIIa activity could not be inhibited by the antithrombin-heparin cofactor, because heparin was protein-bound in tissues and thus did not circulate free in plasma (document (A27)).

Inventive step (Article 56 EPC)

- Document (D9), a report of the Rome conference also attended by Dr Hedner, truly reflected what those skilled in the art were thinking about the factor VIII by-passing activity before the priority date of the patent in suit. Contributions 10, 11 and 13 of document (D9) showed a consensus that the principle responsible for factor VIII bypassing activity in APCC remained unknown or speculative at best.

- Document (D6) did not teach the skilled person to try factor VIIa.

- The skilled person could not deduce from Dr Hedner's oral disclosure that factor VIIa was effective on its own as a haemostatic agent because the dogs to which the preparation had been given neither were haemophilic nor undergoing any bleeding episode.

- Dr Hedner's preparation was not pure factor VIIa since it still contained factor XIIa as a further effective activated clotting agent. The argument of the appellant that Dr Hedner did not remove factor XIIa from her factor VIIa preparation because there was not enough factor XIIa to have any activity *in vivo*, was contradicted by her post-published document (D11), referring to the thrombotic potential of both factor VIIa and factor XIIa. Moreover there was no evidence that factor XIIa in Dr Hedner's preparation would not have had a haemostatic effect on its own.

IX. The Appellant requested in writing that the decision under appeal be set aside and that European patent No. 0 082 182 be revoked. The Respondent requested that the appeal be dismissed and that the patent be maintained.

Reasons for the Decision

Novelty

1. The issue in dispute is whether the intended use made public by Dr Hedner in her oral presentation at the Rome Symposium (see document (D3)) was use of a preparation that meets the technical feature recited in claim 1 that the therapeutic composition should contain factor VIIa as the **sole effective** activated haemostatic agent. This claim does not exclude the presence of activated clotting factors other than factor VIIa (see column 3, lines 17-19 of the patent in suit), and thus the presence of factor XIIa. However, such contaminant factors should not exhibit any clotting activity of their own (*ibidem*, lines 19-29).

2. It has not been disputed by the Appellant that in her presentation at the Rome Symposium (see document (D3)), Dr Hedner said that her factor VIIa preparation contained traces of factor XIIa used in a mass ratio of 1/200 XIIa to VII for activating factor VII to factor VIIa. She did not say that factor XIIa was removed or inhibited and, thus, there is no reason for expecting that the skilled person would do otherwise in repeating Dr Hedner's teaching.

3. A person skilled in the field of blood coagulation would not consider traces of clotting factor as meaningless. This would be contrary to the common

general knowledge in this field that due consideration should always be given to traces of clotting factors because they might trigger important reactions. That traces of clotting factor may be active, transpires from many documents available to the Board, such as document (D9) (see contribution 14, page 112, lines 3-5): "minute amounts of activated factors so minute that they cannot be revealed by conventional assays, might exert their proteolytic action", and document (D13), page 394, lines 17-18, which recites: "Even infinitesimal amounts of thrombin appearing in the product may exert some action". This evidence is in keeping with the passage of document (A10) (see page 375, first two lines) stating that factor VII is a **trace** plasma protein but that it is nevertheless involved in blood coagulation, and with document (A25) (see legend to Table 4 on page 299) showing that traces of thrombin (factor IIa) at a concentration of 0.015 units/ml activate factor VIII. Further, owing to the enzymatic and hence catalytic nature of clotting factors, investigators in this field often take care to inhibit traces of extraneous clotting factors for avoiding false results (see for example, document (D8), page 25, lines 7-8 from the bottom).

4. Dr Hedner and Dr Kisiel stated in their publication (D11) (published after the priority date of the patent in suit) (see page 1837, r-h column, lines 5-7), which comments on the experiments with two dogs, orally reported by Dr Hedner in Rome in 1981 (document (D3)): "No attempt was made to remove the trace amounts of factor XIIa present in the factor VIIa preparation. Accordingly, these studies measured the **thrombotic potential of Factor XIIa** as well as Factor VIIa" (emphasis added). Thus, two experts in haematology such as Dr Hedner and Dr Kisiel lent due consideration to traces of factor XIIa and did not *a priori* exclude that

these trace amounts of factor XIIa could trigger a thrombotic episode in the hosts.

5. In their published work, Dr Hedner and Dr Kisiel do not appear to endorse the appellant's proposition that traces of factor XIIa are meaningless. For the purpose of establishing whether trace amounts of factor XIIa might trigger a clotting reaction, it should be noted that the Board does not see any substantial difference between thrombotic potential and haemostatic potential. A thrombogenic effect can in substance be seen as an unwanted and uncontrollable systemic activation of the coagulation cascade as opposed to haemostasis, which is a therapeutic local clotting process. Depending on the circumstances, a given clotting factor may trigger either haemostasis or a thrombogenic episode. For instance, document (D7), page 1037, lines 1-2, states that factor VIIa might have "therapeutic or thrombogenic potential".

6. In view of this, the Board is satisfied that the composition, which Dr Hedner said she intended to use, would not meet the requirements of claim 1. Accordingly Dr Hedner did not even disclose an intention to use a preparation which would fall within claim 1. Her disclosure in Rome does not destroy the novelty of claim 1.

7. Regarding the alleged novelty destroying use on patients in Stockholm, this was a matter on which the Opposition Division refused to allow into the proceedings written evidence submitted only at the oral proceedings before them by the Other Party, and refused to hear evidence on this point from Dr Hedner, pursuant to their discretion to refuse belated material pursuant to Article 114(2) EPC. In the course of its appeal (since withdrawn) the Other Party again submitted this evidence as well as another affidavit from Dr Hedner

dated 7 September 1992, in which she stated that she made the first treatment of a patient with the preparation she had disclosed in Rome "..on 23rd, 24th and 27th April 1981, as will be seen from the clinical record sheet from my hospital, a copy of which is exhibited hereto as Exhibit UH4. Many persons in my hospital knew what I had done and achieved. There was no need to keep the treatment secret. I had already announced at the Rome Symposium that I would be doing this and that I had suitable patients around all the time." The Appellant relied also on the arguments and evidence of the Other Party, so the Board considers this matter. Unlike for Dr Hedner's disclosure at the Rome Symposium, where there is evidence from witnesses of all parties that Dr Hedner's disclosure was made publicly available, the Board cannot accept that there is adequate evidence before it that the results of the trials at the hospital were made available to the public prior to the publication of Dr Hedner's results (document (D11)) in 1983 after the priority date. The trials at the hospital (unlike the disclosure at the Rome Symposium) were not made for the purpose of informing the public. In these circumstances, the Board cannot accept evidence that the person carrying out the trials believed that she was making the results available to the public already when carrying out the trials, and not only later when publishing her paper, as evidence that it was indeed made available to the public at the time of the trials. Just because Dr Hedner knew exactly what trials she was carrying out, she is not the appropriate witness to state what, if anything, was made available to the public as a result of the trials. She was not in the position of a member of the public, and thus could only make conjectures about what knowledge the public might have acquired. The Board thus does not take these trials in the hospital on human patients into account for the purpose of assessing novelty or inventive step.

8. The findings of points 6 and 7 above also allow novelty to be acknowledged for claims 2 to 15 on the same basis. Although none of method claims 12 to 15 explicitly requires the removal of any activated haemostatic agent which is not factor VIIa, this restriction is implicit by virtue of the direct or indirect reference in these claims to the therapeutic composition according to claim 1, which contains factor VIIa as the sole effective activated haemostatic agent. The method recited in these claims is said merely to "comprise" the explicit steps, so that the inactivation or removal of other haemostatic agent are not excluded.

Inventive step

Introduction

9. Before the priority date of the patent in suit, it was known that blood coagulation was an **exceedingly complex process** in which a number of blood coagulation factors interacted in a series of step-wise reactions, whereby an inactive proenzyme was converted to the active enzymatic form, which in turn converted another proenzyme to its active form (the so-called blood coagulation cascade), the cycle continuing until, as a final step, fibrinogen was converted into fibrin and the fibrin cross-linked. This process was even more complex owing to the presence of modulators and inhibitors taking part in the coagulation cascade, and feed-back effects (ie, some "downstream" clotting factors activating one or more "upstream" factors of the earlier coagulation phases). The coagulation cascade comprised two arms, namely the intrinsic pathway and the extrinsic pathway which converged at the activation of factor X, then merged into a final common pathway up to the end of the coagulation process. Thus, two enzymes were established as activators of factor X to factor Xa, one being the

complex of factor VIII with factor IXa (intrinsic pathway) and the other being the complex between tissue factor and factor VIIa (extrinsic pathway). In the extrinsic pathway, factor VIIa activated factor X into factor Xa without participation of factor VIII (ie, by-passing factor VIII). It was also known that factor VIIa was only active in converting factor X into factor Xa when complexed with the so-called tissue factor, a lipoprotein exposed at the site of tissue damage. Thus, factor VIIa was inactive unless anchored to tissue factor at the site of injury. Therefore, factor VIIa was only active in the extrinsic coagulation system, which was intact in haemophilic patients. In fact, despite their having normal levels of factor VII, patients with haemophilia bled because clotting initiated by tissue factor (ie, the extrinsic pathway) could not compensate for their defect in intrinsic clotting (document (D6), page 837), and thus a normalization of the intrinsic coagulation system was highly desirable.

In the 1960s and 1970s, coagulation factor concentrates became available for treating haemophilia A and B patients. However, about 15% haemophiliacs turned out to develop antibodies against factor VIII or IX. Much effort was placed on finding agents capable of inducing haemostasis by activating the final common pathway of the coagulation cascade, independently of the presence of factor VIII. Activated prothrombin complex concentrates (APCCs) such as Autoplex® and FEIBA®, the latter being an acronym for Factor Eight Inhibitor By-passing Activity, were examples of said agents capable of by-passing factor VIII activity. They comprised a mixture of clotting factors (mainly factor II, ie, prothrombin, and factors V, VII, IX and X) in both activated and zymogen forms and other unknown components and provided some benefit to patients having deficiencies or inhibitors of blood clotting factors.

Such a mixture the Board regards as the closest prior art.

Problem to be solved

10. However, such a prior art mixture besides loading the patient with unnecessary exogenous proteins, could give rise in some patients to dangerous thrombogenic side-effects such as disseminated intravascular coagulation (DIC) or thromboembolic complications. The problem therefore arose of providing a blood clotting preparation that was effective in inducing haemostasis in patients suffering from deficiencies of blood clotting factors or from the presence of inhibitors to blood clotting factors, and had no or fewer side effects than such a mixture.

Solution to the problem

11. The above problem is solved by the therapeutic preparation of claim 1 of the patent in suit comprising factor VIIa as the sole effective activated haemostatic agent. The examples of the patent in suit indeed show that when factor VIIa alone is administrated to haemophilic dogs with bleeding episodes, haemostasis is achieved without giving rise to unwanted thrombogenic side effects. Therefore, the Board is satisfied that the present invention solves the problem as previously set out.

12. Although published after the priority date (1982), document (D9), the proceedings of lectures and papers given at the Rome Symposium on Activated Prothrombin Complex Concentrates held on 30-31 March 1981, can reasonably be taken as truly reflecting what the skilled persons were thinking about the possible by-passing agent(s) in APCCs two months before the priority date of the patent in suit. This document

comprises contributions by six experts or teams taking part in the Rome Symposium and reporting possible theoretical explanations for APCCs efficacy in by-passing factor VIII activity. It emerges from document (D9) that the scientific community had not yet identified the by-passing agent(s) responsible for effectiveness of APCCs in achieving haemostasis. This is shown by the statements made by the experts attending the Rome Symposium on pages 71, 95, 101 to 102 and 115 of the document, according to which there was wide disagreement as to which factors alone or in concert with other unknown serine proteases were responsible for the *in vivo* action. There were many possible mechanisms for haemostasis correction. These mechanisms involved a novel factor Xa-like activity (page 80), a factor VIIICAg-factor IXa-phospholipid complex (paragraph bridging pages 80 and 81), a protease acting through platelets (page 93), a factor VIII coagulant antigen (page 107, lines 3 to 4), an hitherto unidentified factor (or complex) acting directly on the late phase of blood coagulation and activating factor X (page 112, last two lines) or intermediary forms of coagulation factors such as prethrombin 1, prethrombin 2 or some form of factor IXa (page 115, second full paragraph). Document (D9) also mentions that some authors (ie, Dr Seligsohn's team) believed that factor VIIa might play a role in haemostasis correction (paragraph bridging pages 106 and 107). Attractiveness of factor VIIa as a candidate for the effective ingredient of APCCs is also emphasized by document (D15) (see page 118, second paragraph). However, the author thereof also underlines experimental facts against this theory. He came to the conclusion that it was impossible at that time to identify the *in vivo* active components (*ibidem*, last lines). A major problem to be overcome lay in fact with elucidating whether the activated factors assayed in

the plasma after infusion of the APCC were an expression of interactions or simply persisted unmodified in the circulation after infusion. There was no line of action suggested for which there was any reasonable expectation of success, as opposed to a mere hope for success.

13. The Appellant has argued that as the haemostatic properties of factor VII were known since 1956, while the concept of the blood coagulation cascade with its intrinsic and extrinsic pathways, had been introduced in 1964, so the skilled person wishing to by-pass the extrinsic pathway would increase factor VII above physiological levels by added factor VII. The Board disagrees with this line of argument. First, the patent in suit is concerned with factor VIIa, not with factor VII. The use of factor VII is in no way suggestive of factor VIIa since the two molecules perform different functions. Secondly, in the skilled person's mind, the mechanism of factor VIII by-passing activity could have reasonably been explained by the presence in APCCs of one or more activated component(s) from below the block caused by the absence of factor VIII, ie, by "downstream" component(s). Thus, one could have thought of increasing any factor(s) down in the cascade, not necessarily factor VII.

14. APCCs comprised many clotting factors (mainly factor II, V, VII, IX and X) in both activated and zymogen forms in addition to unknown molecules. Given this plethora of components, the skilled persons took very seriously the possibility that more than one component of the APCCs was required for the by-passing effect. This common belief is substantiated by the evidence given hereafter (emphasis added throughout). The authors of document (D6) believed that an activity in the concentrate might activate factor VII to factor VIIa (page 835, line 2 from the bottom) and on

page 836, last paragraph they use the terms "activities" and "**contributes**" suggesting that factor VIIa could require the participation of other factor(s) to achieve haemostasis. Document (D12) also uses the expression on page 7, r-h column, line 10 "the active principle**(s)**". This view is in line with the ones expressed by the experts taking part to the Rome Symposium (see page 79, line 6 from the bottom: "a normalization of the intrinsic system cannot be satisfactorily explained by factor VIIa **alone**"; page 98, lines 5 to 7 from the bottom: "interaction of phospholipids present in APCCs with factor VIIa"; page 121, lines 1 to 3: "factor VIIa and some intermediate form of factor IXa") and is consistent with Dr Hedner's intention to elucidate the haemostatic **role** (not "action") of factor VII (see document (D3)). Also document (D15) on page 118, last paragraph refers to "active components". To conclude this long list, Dr Fujimaki believed that the by-passing activity of FEIBA® required the cooperative effect between factor VIIa **and** factor IXa (see document (A26), page 228, fourth paragraph). Therefore, given the common belief that more than one component of APCCs was responsible for the by-passing activity, there was no incentive to prepare a composition according to claim 1 of the patent in suit with factor VIIa as the sole activated haemostatic agent. The Board has thus to acknowledge this fact as a contribution to the inventive step.

15. As Dr Hedner's presentation to the symposium in Rome (document (D3)) did not comprise any evidence showing success on haemophilic dogs, in the Board's judgement the skilled person who listened to her disclosure would not have had any reasonable expectation of success for a trial of what she suggested, let alone a reasonable expectation of success for a modification of this by excluding activated Factor XIIa.

16. Thus, in the Board's judgement the skilled person would not derive in an obvious manner a therapeutic composition comprising factor VIIa as the sole activated haemostatic agent, from the state of the art. The claims as granted all explicitly or implicitly rely on this feature. Therefore, they satisfy the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairwoman:

D. Spigarelli U. M. Kinkeldey