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# D E C I S I O N
# of 27 February 1998

**Case Number:** T 0913/94 - 3.3.2

**Application Number:** 86108986.0

**Publication Number:** 0207505

**IPC:** A61K 31/12

**Language of the proceedings:** EN

**Title of invention:**
Use of prenyl ketone in the preparation of a medicament against gastritis

**Applicant:**
Eisai Co., Ltd.

**Opponent:**
-

**Headword:**
Agent for gastritis/EISAI

**Relevant legal provisions:**
EPC Art. 56

**Keyword:**
"Inventive step (no) - Second therapeutic application obvious from the prior art"

**Decisions cited:**
-

**Catchword:**

1. The fact that two distinct diseases have the same origin or are elicited by the same causative factors, is not in itself a reason to deny the inventive merit of the second therapeutic application of a known substance.

2. If the manifestations of the second more serious disease are known to run through the manifestations of the first disease, and this assumption reliably substantiated was not confuted, then the activity of a medicament against the more serious disease would already strongly suggest an effect also against the less serious one.

3. Geranylgeranylacetone is known for the treatment of experimentally induced ulcer; its use for the preparation of a medicament for the treatment of gastritis does not involve any inventive merit. (see reasons 3.)

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**Case Number:** T 0913/94 - 3.3.2

**D E C I S I O N**
**of the Technical Board of Appeal 3.3.2**
**of 27 February 1998**

**Appellant:** Eisai Co., Ltd.
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**Representative:** Lehn, Werner, Dipl.-Ing.
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**Decision under appeal:** **Decision of the Examining Division of the European Patent Office posted 8 July 1994 refusing European patent application No. 86 108 986.0 pursuant to Article 97(1) EPC.**

**Composition of the Board:**

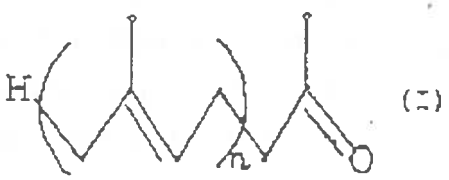
**Chairman:** P. A. M. Lançon
**Members:** C. Germinario
R. E. Teschemacher

## Summary of Facts and Submissions

I. European patent application No. 86 108 986.0 (publication No. 0 207 505) was refused by the examining division on the grounds of lack of inventive step of the subject-matter of claim 1.

The decision was taken on the basis of an independent claim directed to the

"Use of a prenyl ketone compound of formula (I)



(I)

in which n is 3, 4 or 5 for the preparation of a medicament for the treatment or prophylaxis of inflammation of the gastric mucosa".

The following documents, cited during the proceedings, are relevant for the present decision:

(1) Chemical abstracts, Vol. 95, 1981, No. 215545d,

(3) The Merck Manual of Diagnosis and Therapy, 1982, pages 720 to 724,

(5) Japan J. of Pharmacology, 1982, Vol. 32, pages 921 to 924,

(6) Arzneimittelforschung, Vol. 31, No. 5, 1981, pages 799 to 804

II. The examining division, having recognised the novelty of the claimed subject-matter, held that document (1) was not limited to the protecting effect of geranylgeranylacetone (GGA) against ulcer, but related to protection against gastric mucosal damage in general induced by acetylsalicylic acid. Since the skilled person would have included "gastritis" within the meaning of "gastric mucosal damage", he would also have expected a protective effect in relation to gastritis.

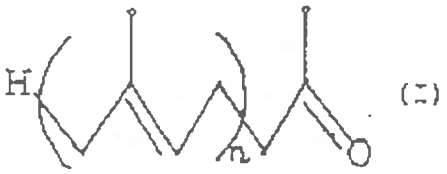
As to the other documents (5) and (6), the examining division pointed out that they disclosed the cytoprotective activity of GGA, which increased the defences of the gastric mucosa against aggressive factors in general. The skilled person would therefore have expected a protective effect not only in the case of ulcer, but in any case of gastric damage, including gastritis.

Finally, keeping in mind that both gastritis and ulcer may be caused by the same aggressive agents, eg aspirin, the examining division expressed the opinion that no alleged difference in the mechanism of outbreak of the diseases could be envisaged to justify any inventive merit in the use of GGA in relation to gastritis.

III. The appellants lodged an appeal against this decision. During oral proceedings on 27 February 1998, an amended single claim was filed.

The claim reads:

"Use of a prenyl ketone compound of formula (I)



in which n is 4 for the preparation of a medicament for the treatment of gastritis resulting from inflammatory lesions of the tunica mucosa ventriculi."

The appellants stressed, in writing and during the oral proceedings, that all the cited prior documents related to experimentally induced ulcer, mainly induced by acetyl salicylic acid; not however to gastritis.

They also argued that gastritis and ulcer were distinct diseases characterised by a different pathology, as recognised by document (3). The wording of the amended single claim should indeed make clear what is meant with the expression "gastritis" and should lay down a threshold between the two pathological states.

To corroborate their position, the appellants underlined firstly that the factors causing gastritis in many subjects were not the organic pathologies typical of ulcer and include psychological, social and environmental aspects. Secondly, that the mechanisms of outbreak of the diseases were different, gastritis developing as inflammation of gastric mucosa, while ulcer through ischemia, necrosis and finally deep degeneration involving the tissues under the mucous membrane too. The different etiological picture of gastritis and ulcer was reflected by the different type

of medicaments used in the two cases. In the appellants' view, no class of medicaments existed, with the exception of the anti-acids, suitable for treating both diseases. In fact, the three leading drugs for peptic ulcer, ie cimetidine, ranitidine and omeprazole, were not used by the medical profession for treating gastritis. Since no consistent parallels occurred between gastritis and ulcer, the only way to discover whether a drug, known for the treatment of ulcer or mucosa damage, could have an effect on gastritis was the clinical investigation, whose results, however, were unpredictable.

IV. The appellants request that the decision of the examining division be set aside and the patent be granted on the basis of the claim submitted in the oral proceedings.

## Reasons for the Decision

1. The amended single claim complies with the requirements of Article 123(2) EPC since the amended features are disclosed on page 2, lines 18, 19, 24 and 25, of the application as filed.

2. *Novelty*

The cited prior art documents (1), (5) and (6) all relate to the treatment with geranylgeranylacetone (GGA) of experimentally induced ulcer or ulcerative damage of the gastric mucosa. However, document (3) makes it clear that ulcer and gastritis represent distinct diseases, though they may occur concomitantly.

On the other hand documents (1), (5) and partially (6) relate to the prophylactic treatment of induced ulcer. Prophylaxis is, however, excluded from the scope of the amended single claim.

As already recognised by the examining division, the subject matter of the valid claim is therefore novel.

3. *Inventive step*

3.1 The appellant has indicated document (6) as the closest prior art document. The board shares this opinion.

This document describes the anti-ulcer effect of the prenyl ketone of the claim, ie geranylgeranylacetone (GGA), on experimentally induced gastric and duodenal ulcers in rats. The document reports that GGA prevents the gastric hexosamine content from its reduction by cold-restraint stress or other aggressive agents. The experimental results suggest that the anti-ulcer activity of GGA is achieved through a mechanism of maintaining the integrity of the mucosal barrier thereby increasing defence efficiency of the gastric mucosa (see the "Summary", item 3.9 and the "Discussion" page 804). Incidentally, these observations are also confirmed by document (5), page 922 to 923.

Moreover, unlike the other cited documents, (6) discloses the use of GGA not only in the prophylactic but also in the curative treatment of ulcer, as illustrated in item 3.6 on pages 802 to 803 and discussed on page 804, left-hand column.

3.2 The underlying technical problem identified in relation to document (6) is to extend the field of therapeutic application of the prenyl ketone of the claim.

The solution proposed by the application under consideration is the use of the compound at issue for the preparation of a medicament for the treatment of gastritis as defined in the claim. The results reported in the clinical instances 1 to 5 in the description prove that teprenone, ie the compound of the claim, is effective in treating gastritis. The board is therefore satisfied that the use according to the claim actually solves the above-identified technical problem.

3.3.1 To assess whether the proposed use of GGA involves an inventive step over the teaching in the closest prior art, document (6), the different aspects, discussed during the proceedings, relating to etiology, mechanism of outbreak and therapeutic treatment of ulcer and gastritis have to be considered, since any possible difference among these aspects may play a decisive role.

3.3.2 In the board's view, though gastritis and ulcer are distinct diseases, they have common aspects in relation to their **causative factors**.

According to document (3), which is a well known text-book illustrating the specific knowledge in 1982, whose teaching is confirmed by other equivalent text-books of the same date, discloses on page 721, under the heading "Acute Gastritis", "Etiology and Pathology" that aspirin or other anti-inflammatory agents can generate gastritis.

The same document discloses under the heading "Peptic Ulcer", "Etiology", on page 724, that certain drugs, such as aspirin and other nonsteroidal anti-inflammatory drugs predispose to formation of an ulcer, though not necessarily a true peptic ulcer. This teaching is confirmed by cited documents (1), (5) and (6), which all describe aspirin or indomethacin (both

nonsteroidal anti-inflammatory drugs) as aggressive agents suitable for inducing experimental ulcer. It is therefore evident that the same aggressive agents may give rise, depending on the intensity and/or length of the stimulus, both to gastritis and ulcer.

The appellants indicated other causes allegedly specific for gastritis, and not for ulcer, such as psychosocial or environmental factors. However, lacking any document able to circumstantiate this statement, the board holds that such factors, like the anti-inflammatory drugs, are also able to cause ulcer, depending on their intensity and length.

3.3.3 The fact that two distinct diseases have the same origin or are elicited by the same causative factors, is not in itself a reason to exclude the protection of a second therapeutic application of a known substance.

Since gastritis and ulcer may be elicited by the same factors, the question remains whether they develop along different and independent **mechanisms** or whether they share the same mechanism, or at least the same decisive steps, which results first in the manifestation of gastritis, then in the more serious manifestation of ulcer.

In fact, while, in the first case, the independence of the mechanisms would preclude any reliable prediction of the effect of a medicament active on ulcer, when applied to gastritis, in the second case, the activity of a medicament against the more serious disease (ulcer) would already strongly suggest that the same medicament could also be effective against the less serious one (gastritis).

Document (3), though not relating to the details of such mechanisms, shows that gastritis, which is normally regarded as a less serious disease than ulcer, is accompanied by manifestations, which in the most serious cases, specifically in the case of acute gastritis, may also include ulcer and mucosal and submucosal haemorrhages. This is taught by the paragraph beginning with "Pathology findings include...", on page 721, which illustrates the typical gastritis symptoms listed by increasing severity. On the other hand, gastritis is usually present in the pathology of peptic ulcer, as reported in the first sentence of page 725, indicating that gastritis is a state which anticipates, and sometimes develops into ulcer.

Still more important is the teaching in (3) that pathological findings of acute gastritis are ischemia and epithelial cell degeneration and necrosis, which, as indicated in the appellants' argumentations, are stages also leading to ulcer.

Summing up, the description given in (3) allows the board to conclude that ulcer does not develop independently of gastritis and according to an exclusive mechanism, which would justify the occurrence of ulcer without any previous occurrence of gastritis, but, on the contrary, that the two diseases develop through the same mechanism, or at least through some common, early stages, on a scale of progressive, increasing severity of symptoms depending on the severity of the aggressive agent.

3.3.4 On this basis, it is to be considered whether, on the priority date of the present application, a (new) anti-ulcer medicament would also have been expected to be active against gastritis. For an answer in the affirmative, a further relevant question is whether, on the priority date, there existed anti-ulcer medicaments known to be effective against gastritis too.

A first class of medicaments common to the two diseases was indicated by the appellants and is cited in (3), namely the anti-acid agents. The board cannot follow the appellants' arguments that "this class represented the unique known family of common medicaments as proved by the fact that the leading drugs for treating peptic ulcer, namely cimetidine, ranitidine and omeprazole were not used by the medical profession for treating gastritis." In fact, according to document (3), page 721, "Prognosis and Treatment", cimetidine was also used with some success in the treatment of acute gastritis. This teaching corresponds to the general common knowledge before the relevant date of the application at issue as proved by other well known text books published in the same period such as "Römpps Chemie-Lexikon", 8th edition, 1981, page 1415 "Gastritis", which cites cimetidine and ranitidine in the treatment of gastritis.

On the priority date of the application, the skilled person was therefore aware that the leading and most widely employed anti-ulcer medicaments, ie anti-acids and H2-histamine receptor antagonists, were also effective against gastritis.

3.3.5 The appellants contested this conclusion arguing that GGA did not belong to any of the two cited classes of medicaments.

While admitting that GGA represents a different class of anti-ulcer medicaments, the board considers this point as immaterial. In the board's judgment, what is decisive is the elucidation, in documents (6) and (5), of the mechanism of action of GGA. This mechanism consists in maintaining the level of mucous hexosamine content in the mucosal barrier protecting the stomach epithelium against its own secretion or any aggressive agent (see (6) item 3.9 and Discussion or (5), page 922 and 923). Being aware of this mechanism, the skilled person would expect that the cytoprotective activity of GGA applies to any kind of attack by a mucous breaker aggressive agent, such as acetylsalicylic acid, regardless of whether it eventually leads to gastritis or ulcer.

Moreover, since the results reported in (6) made it clear that GGA was effective not only in the prophylactic but also in the curative treatment (see "Discussion" in (6)), the protective activity of GGA, either in relation to ulcer or gastritis, would have been viewed by the skilled person not only as the prevention of the decrease of hexosamine content, but also as the restoration of the physiological level of hexosamine content after depletion already induced by aggressive agents, thus as a curative treatment within the meaning of the claim.

3.3.6 In summary, on the priority date of the application at issue, it was known that ulcer and gastritis, though distinct diseases, had common causative factors, developed through common, degenerative states and could be treated with the same medicaments. The skilled person, faced with the technical problem underlying the present invention and assisted by this knowledge, would have regarded gastritis as the most obvious and most promising direction for extending the field of application of the compound disclosed in the closest

prior art, document (6). This choice would have been further motivated by the knowledge of the mechanism of action of GGA which suggested a protective activity not limited to the pathology typical of ulcer but directed, in general, against the action of aggressive factors including those causing gastritis.

For all these reasons, in the board's judgment, the subject-matter of the claim lacks inventive step.

## Order

**For these reasons it is decided that:**

The appeal is dismissed.

The Registrar: The Chairman:

P. Martorana P. Lançon