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Datasheet for the decision of 4 April 2024

Case Number: T 1053/21 - 3.3.02

Application Number: 12744254.9

Publication Number: 2673237

IPC: C07F7/02, C01B39/02, C01B39/46, C01B33/20, A61K33/00, A61K33/24, A61K45/06, A61K9/14, B01J39/02, B01J39/14, B01J19/00, B01J19/18

Language of the proceedings: EN

Title of invention:
USE OF A ZIRCONIUM SILICATE FOR THE TREATMENT OF HYPERKALEMIA

Patent Proprietor:
ZS Pharma, Inc

Opponents:
Teva Pharmaceutical Industries Ltd.
Galenicum Health S.L.U.
Sandoz AG

Headword:
ZS PHARMA / ZIRCONIUM SILICATE / HYPERKALEMIA

Relevant legal provisions:
EPC Art. 123(2), 56

Keyword:
Amendments - added subject-matter (no)
Inventive step - (yes)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1053/21 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 4 April 2024

Appellant: (Opponent 3)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	ZS Pharma, Inc 508 Wrangler Dr., Suite 100 Coppell, TX 75019-7609 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Party as of right: (Opponent 2)	Galenicum Health S.L.U. CL Sant Gabriel n°50 08950 Esplugues de Llobregat (ES)
Representative:	Galenicum Health S.L.U. CL Sant Gabriel n°50 08950 Esplugues de Llobregat (ES)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 10 May 2021 rejecting the opposition filed against European patent No. 2673237 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman M. Maremonti
Members: S. Bertrand
L. Bühler

Summary of Facts and Submissions

I. The appeal by opponent 3 ("appellant") lies from the opposition division's decision to reject the oppositions filed against European patent No. 2 673 237 ("patent").

II. Claim 1 of the patent as granted reads as follows:

"*1. A composition for use in the treatment of hyperkalemia, wherein the composition is a cation exchange composition comprising a zirconium silicate of formula (I)*

$$A_pM_xZr_{1-x}Si_nGe_yO_m \quad (I)$$

where

A is a sodium ion, rubidium ion, cesium ion, calcium ion, magnesium ion, hydronium ion or mixtures thereof,

M is at least one framework metal, wherein the framework metal is hafnium (4+), tin (4+), niobium (5+), titanium (4+), cerium (4+), germanium (4+), praseodymium (4+), terbium (4+) or mixtures thereof,

"p" has a value from 1 to 20,

"x" has a value from 0 to less than 1,

"n" has a value $0 < n \leq 12$,

"y" has a value from 0 to 12,

"m" has a value from 3 to 36 and $1 \leq n + y \leq 12$,

wherein the composition exhibits a median particle size of greater than 3 microns and less than 7% of the particles in the composition have a diameter less than 3 microns, and the composition exhibits a sodium content below 12% by weight."

III. The following documents are used in the present decision:

D3 WO 02/062356 A2

D12 US 6,579,460 B1

D13 O'Hagan, D. T., Advanced Drug Delivery Reviews, 5 (1990), pages 265-285

D14 Florence, A. T., Drug Discovery Today: Technologies, 2 (2005), pages 75-81

D15 Information on ZS Pharma website, published on 6 September 2010

D29 Extract from FDA Chemistry Review of Lokelma®, quality assessment section (NDA 207078)

A032 Lokelma® assessment report, European Medicines Agency, 25 January 2018

A033 Experimental report, "Sodium Zirconium Cyclosilicate Particles: Size Dependent Uptake in Rats *In Vivo*", 20 January 2022

IV. In the impugned decision, the opposition division's conclusions included the following.

- The ground for opposition under Article 100(c) EPC did not prejudice the maintenance of the patent as granted.

- The subject-matter of the claims of the patent as granted involved an inventive step in view of D3 or D15 as the closest prior art.

V. In its statement of grounds of appeal, the appellant contested the opposition division's reasoning and challenged, *inter alia*, the inventive step of the subject-matter of claim 1 as granted in view of D3 or D15 as the closest prior art. The appellant corroborated its arguments by submitting *inter alia* document A032 (denoted D32 by the appellant).

VI. In its reply to the grounds of appeal, the patent proprietor ("respondent") provided counter-arguments to the appellant's objections. It submitted sets of claims according to auxiliary requests 1 to 23. In response to document A032 filed by the appellant, the respondent filed A033 (denoted D33 by the respondent).

VII. Opponents 1 and 2 did not file any submissions or submit any requests. Opponents 1 and 2 were parties as of right to these proceedings. Opponents 1 and 2 announced that they would not be attending the oral proceedings.

VIII. The board summoned the parties to oral proceedings as per their requests and issued a communication under Article 15(1) RPBA.

IX. Oral proceedings before the board were held by videoconference on 4 April 2024, in the presence of the appellant and respondent and in the absence of opponents 1 and 2 in accordance with Rule 115(2) EPC. During the oral proceedings, the respondent made auxiliary request 2 its main request. The previous main request (patent as granted) and auxiliary request 1 were made auxiliary requests 1 and 2, respectively.

X. The parties' requests, where relevant to the decision, were as follows.

The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety. It also requested that document A033 not be admitted into the proceedings.

The respondent requested that the decision under appeal be set aside and the patent be maintained in amended form on the basis of the claims of the main request filed as auxiliary request 2 with the reply to the appeal.

XI. The appellant's case and the respondent's case, in so far as relevant to the present decision, are summarised in the Reasons below.

Reasons for the Decision

Main request (filed as auxiliary request 2 with the reply to the appeal)

1. Added subject-matter (Article 123(2) EPC) - claim 1

1.1 Claim 1 of the main request reads as follows:

"*1. A composition for use in the treatment of hyperkalemia, wherein the composition is a cation exchange composition comprising a zirconium silicate of formula (I)*

$$A_pM_xZr_{1-x}Si_nGe_yO_m \qquad (I)$$

where

A is a sodium ion, rubidium ion, cesium ion, calcium ion, magnesium ion, hydronium ion or mixtures thereof,

M is at least one framework metal, wherein the framework metal is hafnium (4+), tin (4+), niobium (5+), titanium (4+), cerium (4+), germanium (4+), praseodymium (4+), terbium (4+) or mixtures thereof,

"p" has a value from 1 to 20,

"x" has a value from 0 to less than 1,

"n" has a value $0 < n \leq 12$,

"y" has a value from 0 to 12,

"m" has a value from 3 to 36 and $1 \leq n + y \leq 12$,

wherein the ***zirconium silicate of formula (I)*** ~~*composition*~~ *exhibits a median particle size of greater than 3 microns and less than 7% of the particles in the composition have a diameter less than 3 microns, and the* ***zirconium silicate of formula (I)*** ~~*composition*~~ *exhibits a sodium content below 12% by weight*." (Emphasis added by the board; strike through and bold text represent deletions and additions, respectively, compared with claim 1 as granted.)

1.2 The appellant asserted that the amendment in claim 1 of the main request identified above introduced subject-matter which was not disclosed in the application as filed. More particularly, it argued that the median particle size, the sodium content and the feature that less than 7% of the particles in the composition have a diameter less than 3 microns were disclosed in the application as filed only with respect to the "composition" as such and not with respect to the "zirconium silicate of formula (I)".

1.3 The board disagrees.

As submitted by the respondent, it is clear from the application as filed that the median particle size, the sodium content and the feature that less than 7% of the particles in the composition have a diameter less than 3 microns relate to the zirconium silicate of formula (I).

Firstly, the first paragraph of page 5 of the application as filed states that "[t]*he inventors have discovered novel zirconium silicate molecular sieves to address the problem associated with existing hyperkalemia treatments, and novel methods of treatment for hyperkalemia utilizing these novel compositions*". The term "*these novel compositions*", used with respect to the claimed invention, refers to the zirconium silicate molecular sieves and nothing else.

Furthermore, on page 5 of the application as filed, under "*Summary of the invention*", reference is made first to the zirconium silicates of formula (I). According to the embodiment in the last paragraph on page 5, **the composition** exhibits a median particle size of greater than 3 microns, and less than 7% of the particles in the composition have a diameter less than 3 microns. In view of the use of the definite article "the", the composition in the last paragraph on page 5 clearly refers to the zirconium silicates of formula (I) mentioned previously on page 5. The second full paragraph on page 6 of the application as filed discloses a further embodiment and refers to "the composition" exhibiting the median particle size, the fraction of particles in the composition having a diameter less than 3 microns defined previously, and a sodium content of below 12% by weight.

Moreover, the second paragraph on page 19 of the application as filed refers to a method of preparing the zirconium silicates of formula (I). Particles having a diameter below 3 microns are removed by screening. Once again, reference is made in this paragraph to a zirconium silicate composition exhibiting "*a median particle size of greater than 3 microns*" and in which "*less than 7% of the particles ... have a diameter less than 3 microns*". This composition is clearly the zirconium silicate of formula (I) because no other "composition" or "particles" are disclosed in this passage of the application as filed.

Examples 6 and 7 of the application as filed disclose the preparation of zirconium silicate powders (H-ZS-9) having the desired sodium content. These examples thus confirm that the sodium content is related to the zirconium silicate of formula (I).

Example 9 of the application as filed discloses the screening of zirconium silicate of formula (I). It is clearly disclosed that different particle size distributions may be obtained for the zirconium silicate ZS-9 using screens of different sizes (bottom of page 26). Example 9 thus confirms the disclosure of the application as filed that the median particle size of greater than 3 microns and the feature that less than 7% of the particles in the composition have a diameter less than 3 microns pertain to the zirconium silicate of formula (I).

In view of the above, the board concludes that the amendment made in claim 1 of the main request identified above is based on the application as filed. The basis for the remaining features of claim 1 is the

combination of claims 1 and 21 as filed. Therefore, the requirements of Article 123(2) EPC are met.

2. Inventive step (Article 56 EPC) - claim 1

2.1 According to paragraph [0004] of the patent, acute hyperkalemia results from elevated serum potassium levels.

According to paragraph [0005] of the patent, "[s]*ymptoms of hyperkalemia are somewhat non-specific and generally include malaise, palpitations and muscle weakness or signs of cardiac arrhythmias, such as palpitations, bradytachycardia or dizziness/fainting*".

The patent is concerned with the use of microporous zirconium silicate compositions for treating hyperkalemia that are formulated to remove toxins, e.g. potassium ions, from the gastrointestinal tract at an elevated rate without causing undesirable side effects (paragraph [0001] of the patent).

2.2 The appellant challenged the inventive step of the subject-matter of claim 1 of the main request starting from D3 or D15.

2.3 D3 as the starting point

2.3.1 D3 relates to compounds and methods for treating patients exhibiting high levels of serum toxins, by administering to such patients a zirconium silicate sorbent in amounts sufficient to reduce one or more of the levels of the serum toxins.

Example 2 of D3 (page 20), relied on by the appellant, discloses *in vivo* tests on rats for measuring the chemical effectiveness of dried powdered zirconium

silicate incorporated in the food administered to the rats. The dried powdered zirconium silicate has a "*5-10 micron particle size*" (page 21, lines 9-13). Furthermore, the dried powdered zirconium silicate is "*100% sodium-loaded*" (page 23, lines 23 and 24).

It was not disputed that the dried powdered zirconium silicate used in example 2 of D3 is a compound of formula (I) according to claim 1 of the main request.

On the basis of the "*100% sodium-loaded*" disclosure on page 23, lines 23 and 24 of D3, the sodium content of the zirconium silicate in example 2 of D3 cannot be calculated.

2.3.2 The appellant submitted that the particle size of 5-10 microns disclosed in example 2 of D3 defined the absolute particle size and that the average particle size disclosed in example 2 of D3 would inevitably be within the preferred range of the average particle size defined on page 12, lines 2 and 3 of D3. This implied a median particle size of greater than 3 microns and also that less than 7% of the particles had a diameter less than 3 microns, as required by the cation exchange composition of claim 1 of the main request.

2.3.3 The board disagrees.

It cannot be concluded that example 2 of D3 discloses an absolute particle size of 5-10 microns since there is no indication anywhere in D3 that the particle size of 5-10 microns in example 2 of D3 was intended to be an absolute particle size. On the contrary, the paragraph bridging pages 11 and 12 of D3 discloses that "... *the zirconium-silicate of the present invention is provided as fine powder having an average particle size*

between about 3 to about 50 microns, more preferably between about 5 and about 10 microns". Thus, in view of this disclosure, the particle size of 5-10 microns referred to in example 2 of D3 is an average particle size. This average particle size of 5-10 microns implies a median particle size of greater than 3 microns, as required by claim 1 of the main request.

However, there is no correlation between the average particle size and the particle size distribution. In other words, an average particle size of 5-10 microns does not necessarily imply that less than 7% of the particles have a diameter less than 3 microns.

2.4 Distinguishing features

In view of the above, the distinguishing features of the subject-matter of claim 1 of the main request over example 2 of D3 are at least that the sodium content is below 12 wt.% and less than 7% of the particles in the composition have a diameter less than 3 microns.

2.5 Technical effects achieved by the distinguishing features

The respondent relied on D29 and paragraphs [0001], [0013], [0043]-[0046] and [0052] of the patent for assessing the technical effects achieved by the distinguishing features.

Paragraphs [0013] and [0045] of the patent referred to by the respondent essentially explain that the adverse effects of systemic absorption of zirconium silicate compositions are mixed leucocyte inflammation, urinary bladder inflammation and accumulation of particles in the patient's urinary tract and kidneys leading to

toxicity. These adverse effects are reduced by limiting the number of particles having a diameter less than 3 microns in the composition.

Paragraphs [0043] and [0044] of the patent teach that a reduced sodium content in the zirconium silicate composition reduces adverse effects arising from an increase in urine pH.

Paragraphs [0001], [0046] and [0052] of the patent disclose that the above adverse effects are reduced by the claimed compositions, characterised by the feature that less than 7% of the particles in the composition have a diameter less than 3 microns and by the specific sodium content, i.e. less than 12% by weight.

D29 is a post-published extract from the American Food and Drug Administration's Chemistry Review for Lokelma®, a drug comprising sodium zirconium silicate (point 2 on page 2). According to D29, very fine particles can lead to the systemic absorption of sodium zirconium silicates. The limit on the number of small particles of zirconium silicate was established on the basis of a safety consideration. As a result, a limit on particles below 3 microns was fixed at 3% (top of page 4). D29 thus confirms that the adverse effect of systemic absorption of zirconium silicate is reduced when the content of particles below 3 microns in the zirconium silicate composition is limited.

The appellant disputed the technical effects mentioned above.

First, the appellant submitted that an alleged advantageous technical effect of an invention could not

be based on a purely theoretical assumption without any scientific justification or experimental evidence.

This argument is not convincing. As set out above, D29 sets a limit on particles below 3 microns at 3% (top of page 4) for safety considerations. For this reason, the reduction of systemic absorption, referred to in the patent and associated with the limit on particles below 3 microns, is based on a scientific justification represented by D29 and is thus not a purely theoretical assumption, contrary to the appellant's submission.

Second, the appellant submitted that the patent did not present any experimental evidence whatsoever demonstrating that the alleged technical effect of reduced side effects was actually achieved. D29 could not evidence the effect alleged in the patent since the experimental basis on which the claimed particle size limit of 3 microns was chosen was not known, so the limit was instead purely arbitrary.

The board is not convinced. As set out above, D29 clearly teaches that very fine particles can lead to the systemic absorption of sodium zirconium silicate. As submitted by the respondent, the 3-micron limit in claim 1 of the main request is included to reduce the size of the particles which are more likely to affect safety, as established by D29. The particle size limit of 3 microns in claim 1 of the main request is thus not arbitrary.

Furthermore, the appellant submitted that no comparison with the closest prior art D3 had been provided and no technical effect resulting from the distinguishing features of claim 1 had been demonstrated.

The board disagrees. As submitted by the respondent, it is irrelevant that no direct comparison with the closest prior art D3 has been provided. As set out above, D29 confirms the advantageous effect of a distinguishing feature of the claims, i.e. that the number of smaller particles needs to be restricted due to potential safety concerns. It is therefore implicit that compositions with a lower fraction of particles having a diameter less than 3 microns, e.g. less than 7% as required by claim 1 of the main request, exhibit a lower safety risk when compared with a comparable composition having more than 7% of particles with a diameter less than 3 microns. This lower safety risk is thus attributable to the feature that less than 7% of the particles in the composition have a diameter less than 3 microns, as required by claim 1 of the main request.

Lastly, the appellant submitted that according to A032, the alleged safety was not an effect resulting from the feature that less than 7% of the particles in the composition have a diameter less than 3 microns. It was not this feature which was responsible for the non-absorption of zirconium silicate, as stated in D29, but instead it was the insolubility of the zirconium silicate that achieved this effect. Hence, D29 provided contradictory information to that provided in A032.

The board is not convinced for the following reasons. A032 is the Lokelma® assessment report, on which the European marketing authorisation of Lokelma® (drug comprising sodium zirconium silicate referred to in D29) is based. A032 discloses on page 16 that "[t]*he applicant stated that ZS* [zirconium silicate] *is not expected to be absorbed due to its* ***insolubility*** *and no interactions with secondary targets are expected.*

Hence, no in vitro secondary pharmacodynamic studies have been conducted. This is acceptable to the CHMP" (emphasis and text in square brackets added by the board). In addition, A032 discloses in item 2.3.3. on page 17 that "[d]*ue to its inorganic composition, sodium zirconium cyclosilicate, is not subject to enzymatic metabolism and due to* ***its insolubility and particle size*** *it is in* [sic] *not a substrate for transporter processes, has no effect of cytochrome P450 metabolism or induction* ***and is systemically not absorbed****. The lack of any significant absorption is confirmed by analysis of dog whole blood and urine in which no Zr could be detected following 9 months of daily administration of sodium zirconium cyclosilicate ...*", and on page 47 (first paragraph) that "*there is no significant systemic absorption as would be expected for an insoluble material* ***with this particle size***" (emphasis added by the board).

Thus the above-cited passages of A032 precisely teach that the particle size in addition to insolubility is an important factor which was adjusted to reduce the risk of systemic absorption. This is entirely in line with the patent, which teaches that while zirconium silicates are essentially insoluble (last sentence of paragraph [0016]), there is still some risk of systemic absorption of small particles. This risk can be reduced by changing the particle size distribution (paragraph [0045]), i.e. by the feature that less than 7% of the particles in the composition have a diameter less than 3 microns.

2.6 Objective technical problem

In view of the above, the objective technical problem is to provide a safer composition for use in the

treatment of hyperkalemia, as formulated by the respondent.

2.7 Obviousness

The appellant relied on D3 itself, the common general knowledge represented by D13 and D14, and D12, all of which gave a pointer towards the claimed solution.

However, the board notes that D3 does not provide any teaching whatsoever about the risks associated with the systemic absorption of zirconium silicate compositions, let alone with the absorption of particles having a diameter less than 3 microns.

D13 (page 266, last paragraph) discloses that "[t]*he potential uptake of particles across the GIT* [gastrointestinal tract] *is an important phenomenon which may have toxicological, immunological and pathological implications*". In addition, D13 (table 1 on page 267) discloses mechanisms for the uptake of particulates across the gastrointestinal tract and identifies the size range of the absorbed particulates. D13 does not disclose any zirconium silicate composition.

D14 (page 75, first full paragraph of the right-hand column) discloses that "[i]*t is generally agreed that absorption increases with decreasing particle diameter. Studies on polystyrene latex (a useful model because of nonbiodegradability) in the range of 3 µm to 50 nm [3] revealed that maximal absorption occurred with particles ranging 50–100 nm in diameter*". D14 does not disclose any zirconium silicate composition.

In fact, D13 and D14 concern the potential benefits of delivering drugs by loading them onto microparticles (D13, summary on page 266; D14, conclusions on page 80). D13 and D14 are not related to safety concerns associated with systemic exposure to microparticles. On the contrary, their aim is to maximise this systemic exposure because the microparticles are intended to be drug delivery systems for systemic use. This is the opposite goal to the patent.

Thus, neither D13 nor D14 relates to zirconium silicate compositions, let alone to the potential safety issues associated with their absorption.

D12 relates to the pharmaceutical use of zirconium silicate cation exchangers for removing toxins from blood or dialysate solutions (abstract of D12). The UZSi-9 of example 2 is a zirconium silicate having a particle size of 20-50 µm, i.e. a particle size according to claim 1 of the main request. However, D12 is not concerned with either the systemic absorption of zirconium silicate particles or associated potential safety issues.

None of the above documents cited by the appellant (D3, D12, D13 and D14) provides the teaching that the fraction of zirconium silicate particles having a diameter less than 3 microns should be limited to avoid safety issues linked to their systemic absorption. Thus, these documents fail to provide teaching that would lead the skilled person to the claimed invention when faced with the objective technical problem identified above.

Therefore, the board concludes that the subject-matter of claim 1 of the main request involves an inventive step when starting from D3 (Article 56 EPC).

3. D15 as the starting point

3.1 D15 discloses the zirconium silicate product UZSi-9 as an oral sorbent for use in the treatment of hyperkalemia. D15 does not disclose the median particle size of the particles, the fraction of particles in the UZSi-9 product having a diameter less than 3 microns, or the sodium content.

3.2 Hence, claim 1 of the main request comprises the same distinguishing features in view of the disclosure of D15 as those identified when starting from D3.

The same problem-solution approach as that established starting from D3 thus applies when starting from D15.

3.3 Therefore, the subject-matter of claim 1 of the main request also involves an inventive step when starting from D15 (Article 56 EPC).

4. In arriving at the above conclusions starting from D3 or D15, the board did not take into account document A033 of the respondent. There was thus no need for the board to decide on the admittance of A033, which had been contested by the appellant.

5. The appellant did not raise any further objections against the claims of the main request.

6. It follows that the main request is allowable.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent on the basis of claims 1 to 13 of the main request filed as auxiliary request 2 with the reply to the appeal, and the description and drawings to be possibly adapted thereto.

The Registrar: The Chairman:

I. Aperribay M. Maremonti

Decision electronically authenticated