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Datasheet for the decision of 17 July 2014

Case Number: T 0210/11 - 3.3.07

Application Number: 02796109.3

Publication Number: 1455756

IPC: A61K9/14, A61K9/16, A61K9/51, A61K31/5377

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL NANOPARTICULATE COMPOSITION OF A TACHYKININ RECEPTOR ANTAGONIST

Patent Proprietor:
Merck Sharp & Dohme Corp.

Opponents:
Hexal AG
Teva Pharmaceutical Industries Ltd.

Headword:
PHARMACEUTICAL NANOPARTICULATE COMPOSITION OF A TACHYKININ RECEPTOR ANTAGONIST/Merck Sharp & Dohme

Relevant legal provisions:
EPC Art. 123(3), 123(2), 84, 100(b), 54, 56

Keyword:
Amendments - broadening of claim (no) - added subject-matter (no)
Claims - clarity - main request (yes)
Grounds for opposition - insufficiency of disclosure (no)
Novelty - (yes)
Inventive step - (yes)
Reimbursement of appeal fee - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
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Case Number: T 0210/11 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 17 July 2014

Appellant: (Opponent 1)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	von Seebach, Malte Maiwald Patentanwalts GmbH Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 5 Basel Street, P.O. Box 3190 Petah Tiqva 49131 (IL)
Representative:	Gallagher, Kirk James D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Patent Proprietor)	Merck Sharp & Dohme Corp. 126 East Lincoln Avenue Rahway, NJ 07065-0907 (US)
Representative:	Man, Jocelyn Merck & Co., Inc. European Patent Department Merck Sharp & Dohme Limited, Hertford Road, Hoddesdon Hertfordshire, EN11 9BU (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 December 2010 concerning maintenance of the European Patent No. 1455756 in amended form.**

Composition of the Board:

Chairman	J. Riolo
Members:	D. Boulois
	P. Schmitz

Summary of Facts and Submissions

I. European patent No. 1 455 756 based on application No. 02 796 109.3 was granted on the basis of a set of 15 claims.

Independent claim 1 as granted read as follows:
"1. A nanoparticulate composition comprising the compound 2- (R)- (l- (R)- (3, 5-bis (trifluoromethyl) phenyl) ethoxy)-3- (S)- (4-fluoro) phenyl-4- (3- (5-oxo-lH, 4H-1, 2, 4-triazolo) methylmorpholine, or a pharmaceutically acceptable salt thereof, the compound having adsorbed on the surface thereof at least one surface stabilizer in an amount sufficient to maintain an effective average particle size of less than about 1000 nm."

II. Two oppositions were filed against the granted patent. The patent was opposed under Article 100(a), (b) and (c) EPC, on the grounds that its subject-matter lacked novelty and inventive step, the patent was not sufficiently disclosed and its subject-matter extended beyond the content of the application as filed.

III. The documents cited during the opposition and appeal proceedings included the following:
(1) WO00/10545
(3) US 6 235 735
(4) J. of Med. Chemistry, 2000, 43(6), 1234-1241
(5) US 6 267 989
(6) EP 0 499 299
(7) US 5 591 456
(9) US 6 096 742
(14) Int. J. of Pharm., 285(2004), pages 135-146
(15) Remington: The Science and Practice of Pharmacy (191th Edition), pages 135-146

(16) “Dispersions, Characterisation, Testing and Measurement”, 1999, M.Dekker, Chapter 2, pages 17-18, 37-41
(17) Jamzafat et al, AAPS Pharm. Sci. Tech., 2006, 7(2), Article 33
(18) “Dynamic Light Scaterring”, pages 1-8, obtained from the homepage of Malvern Instruments

IV. The present appeal by opponents 01 and 02 lies from the decision of the opposition division to maintain the patent as amended. The decision was based on 2 sets of claims filed with letter of 30 November 2009 as main request and auxiliary request 1 filed during oral proceedings on 28 October 2010.

Independent claim 1 of the main request and auxiliary request 1 read:
"1. A nanoparticulate composition comprising the compound
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, or a pharmaceutically acceptable salt thereof, the compound having adsorbed on the surface thereof at least one surface stabilizer in an amount sufficient to maintain an effective average particle size of less than about 1000 nm; where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm."

Auxiliary request 1 differed from the main request by the suppression of claims 9-13, the subject-matter of claims 1-8 being identical to the subject-matter of claims 1-8 of the main request.

V. According to the decision under appeal, the subject-matter of the main request met the requirements of Article 123(2) EPC.
The fact that claim 1 of the main request did not refer to "*the above noted techniques*" for measuring the particle size did not contravene Article 123(2) EPC.
Moreover, the combination of the subject-matter of claim 7 with any of the features of claims 2-5 did not contravene Article 123(2) EPC either, as its disclosure at page 8 in the description was considered to be a general disclosure.

The terms "*1000 nm*", "*by weight*" and "*about*" in claim 1 of the main request were considered to meet the requirements of Article 84 EPC.

As regards disclosure, the skilled man was aware that different measuring techniques would lead to different results in terms of particle size, and it laid in his field of competence to choose the appropriate method according to the actual measure to carry out. The skilled man was also in a position to adapt the measurement of the particle size by volume according to the dynamic light scattering technique and to derive the corresponding value by weight, by using the value of the density of the compound/composition to be measured.

The opposition division considered that document (1) did not anticipate the subject-matter of claim 1, as it disclosed the drug 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1H,4H-1,2,4-triazolo)methylmorpholine, whose chemical name is **aprepitant**, only in the description on page 4, lines 25-26 as one possible active substance.

As regards inventive step, the closest prior art was document (3) which disclosed compositions comprising aprepitant, without any disclosure of a nanoparticulate composition having a surface stabilizer adsorbed on its surface.
The technical effect linked with said feature was an enhanced bioavailability of aprepitant.
Document (14) provided evidence of this effect.
Document (5) described that reducing particle size of a poorly water soluble drug to a value between 150 and 350 nm and adding one or more surface stabilizers adsorbed on the surface of said drug would increase its stability which in turn would lead to a reduction of particle aggregation and crystal formation, thereby leading to an increased bioavailability. Document (5) did not give any indication that aprepitant could benefit from this procedure.
The subject-matter of claims 1-8 of the main request was considered as inventive.

However, the subject-matter of claims 9-13 of the main request was not considered to be inventive.

Since the subject-matter of auxiliary request 1 corresponded to claims 1-8 of the main request, this request was considered to be inventive.

VI. Opponents 01 and 02 filed an appeal against said decision.
They requested that the decision be set aside and the patent be revoked.
Additionally, they requested reimbursement of the appeal fee in light of a substantial procedural violation committed by the opposition division.

VII. With a letter dated 25 October 2011, the respondent requested that the appeals be dismised.
Additionally, the respondent contested the admissibility of the appeal of appellant 01, and submitted further arguments regarding Articles 123(2) and 123(3) EPC, clarity, sufficiency, novelty and inventive step.
The respondent submitted as well a new document:
(19) Particle size conversion, Sigma-Aldrich.

VIII. With a letter dated 28 March 2012, opponent-appellant 01 submitted further arguments and a new document:
(20): Encyclopedia of Chemical Technology, 1997, volume 22, 256-278

IX. A Board's communication dated 4 July 2014 was sent to the parties.

X. With a letter dated 7 July 2014, the respondent submitted auxiliary requests 1 and 2.

XI. Oral proceedings took place on 17 July 2014.

XII. The arguments of the appellants, as far as relevant to the present decision may be summarized as follows:

Main Request - Article 123(3) EPC

According to appellant 02, through the introduction of the feature *"where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm"*, the subject-matter of amended claim 1 of the main request was broader than the claim as granted, since it required only that 95% of the particles have an average particle size of less than

1000 nm, this leaving 5% of the aprepitant particles of unspecified particle size. The overall population could thus have an effective average particle size greater than 1000 nm.

Main Request - Article 123(2) EPC

According to appellant 02 the statement *"where effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm"* introduced in claim 1, could find a basis in the description on page 19, lines 25-27 and 30-31, but only in conjunction with the term *"when measured by the above noted techniques"*. According to appellant 02, the omission of this feature deprived the amendment from its basis in the description. Since claim 1 of the main request did not specify that the measurement had to be carrier out by specific methods, it allowed not for any method to be used which may give different results. This was demonstrated by document (16).

Main Request - Article 100(b) EPC

According to appellant 01, the contested patent did not give any guidance to the skilled person how a sample of the claimed composition with the effective average particle size was obtained.
As disclosed by document (18), the diameter measured by DLS was a value that depended not only on the size of the particle core, but also on its surface structure, as well as, *inter alia*, the concentrations and type of ions in the medium of measurement. The sample preparation and measurement conditions were crucial for a reliable determination of the average particle size.

Accordingly, the person skilled in the art was not enabled by the disclosure of the patent to determine correctly the average particle size, and thus to put the claimed composition into practice.
In addition, it was crucial to the skilled person to know which method is used for determining the effective average particle size. In paragraph[0078] of the contested patent, conventional methods were mentioned, but they would provide different particle sizes.

Appellant 02 was also of the opinion that different methods of measurement would have given rise to different results, and the method chosen had a significant influence on the final result achieved. Document (18) showed also that it was not possible to provide a weight average particle size with the dynamic light scattering method (DLS).

Main Request - Article 84 EPC

According to appellant 01, the definition "*where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm"* was not present in the granted claims and lacked clarity. The skilled person was not in a position to determine said effective average particle size, through the absence of any measurement method in the description or in common general knowledge. The same objection applied to the measurement of the size "*by weight*", since none of the methods given in the description could be used for measuring a size by weight.
Moreover, the only method given in the description in paragraph [0078] applied only to liquid dispersions.
Moreover, the term "*less than about 1000 nm*" was

indefinite because it simultaneously claimed two different ranges.
As the term *"where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm"* was not contained in the granted claims, the upheld claims had to be examined as to their compliance with all requirements of the EPC, including Article 84 EPC.

Main Request - Novelty

According to appellant 01, document (1) was novelty destroying, since examples 1 to 4 disclosed generic compositions in which the active agent was not specified, but suitable for any of the active agents disclosed in this document, namely also aprepitant (MK869), disclosed on page 4, lines 3 to 4.

Main Request - Inventive step

The appellants agreed that document (3) should be the closest prior art.

According to appellant 01, the claimed subject-matter differed in the feature that aprepitant is provided as a nano-particulate composition having absorbed on its surface a surface stabilizer.
The objective problem was seen as how to increase the bioavailability of aprepitant.
Document (5) disclosed nano-particulate compositions with surface stabilizers. The skilled person would apply the teaching of document (5) to aprepitant, since it was a poorly soluble drug. Moreover, document (5) taught that the procedure was suitable for anti-emetics drugs.

The same incentive could be found in documents (6) or (7).
The increase of bioavailability was thus an expected effect in view of these documents, and document (14) did not need to be considered, since it only confirmed what was expected by the skilled person.
Moreover, document (14) disclosed in paragraph 3.4 that the redispersion of the nano-particulates, and thus the bioavailability of aprepitant, could be affected by their formulation in a solid dosage form.

According to appellant 02, the increase of oral bioavailability could not be seen as a plausible technical effect, since no supporting evidence was offered in the patent in suit. It was also inappropriate to rely on post published evidence, such as document (14), to support an inventive step.
It was true that document (14) demonstrated that a decrease in particle size of aprepitant led to an increase of dissolution and hence bioavailability. This was however the result of a very basic concept in chemistry and was obvious for this reason, as shown by document (15).
As regards the reduction of the food-effect shown by document (14), this effect was speculative and could not be linked with the problem stated in the patent, namely the increase of bioavailability. This effect could only be seen as a *"bonus effect"*.
Document (5) disclosed the addition of surface stabilizers to nano-particulate of poorly soluble drugs, such as anti-emetics or anxiolytics, to increase the bioavailability. As aprepitant had these pharmacological properties, there was a clear incentive to apply the teaching of document (5) to said aprepitant.

Reimbursement of the appeal fee

The ground on the basis of Article 123(3) EPC was raised by appellant 02 for the first time during the oral proceedings before the opposition division, and was not admitted by the opposition division into the proceedings, because it was a late-filed and *prima facie* irrelevant ground.
The written decision of the opposition division however barely referred to the issue and did not give any explanation and reasons as to why the objection was not considered *prima facie* relevant.
Appellants 01 and 02 saw in the absence of any reference in the written decision of the opposition division regarding its decision to not admit the ground of Article 123(3) EPC into the proceedings a substantial procedural violation.

XIII. The arguments of the respondent, as far as relevant to the present decision, may be summarized as follows:

Admissibility of the appeal by appellant 01

The appeal filed by the notice dated 25 January 2011 should have been deemed inadmissible for failure to identify the appellant or for having been filed in the name of a party not entitled to appeal. There was no identification or indication that the appeal was filed on behalf of one of the opponents.

Main Request - Article 123(3) EPC

The amendment brought to claim 1 of the main request reduced the scope of the claim. The amendment made explicit what was already implicit in the claim. There could not be any broadening of the subject-matter.

Main Request - Article 123(2) EPC

As to the omission of the term "*the above noted techniques*" in claim 1 as reference to the methods of measurement mentioned in paragraph [0078] of the description, all "*the above noted techniques*" were "*conventional techniques well known to the the person skilled in the art*", as disclosed in said paragraph [0078], and one was not restricted to the use of any particular measuring technique. There was thus no reason to add a restriction on a specific measurement technique.

Main Request - Article 100(b) EPC

Characterization of pharmaceutical dispersions by particle size analysis belonged to common general knowledge. The definition of claim 1 together with the description was perfectly adequate for the skilled person.

Main Request - Article 84 EPC

The objections of lack of clarity made against the absence of any method of measurement of the average particle size in the claim and to the presence of the term "*about*" were not linked with amendments made during the opposition procedure. The objections under Article 84 EPC were thus not properly made.

Main Request - Novelty

Document (1) cannot be considered as novelty destroying, since the examples of this document do not identify aprepitant as active agent.

Main Request - Inventive step

Document (3) could be seen as the closest prior art. The teaching of document (14) had to be taken in account, since it provided evidence of unexpected technical effects.

XIV. The appellants (opponents 1 and 2) requested that the decision under appeal be set aside and that the patent be revoked. The appellants additionally requested that the appeal fee be reimbursed.

XV. The respondent (patent proprietor) requested that the appeals be dismissed, or in the alternative that the patent be maintained according to auxiliary request 1 or 2 filed by letter of 7 July 2014.

Reasons for the Decision

1. The appeal of appellant 02 is admissible.

2. Admissibility of the appeal of appellant 01

The admissibility of the appeal formed by appellant 01 has been contested by the respondent, because in the notice of appeal no name was given for he appellant.

The notice of appeal indeed did not mention the appellant's name, but referred only to the patent number and the corresponding patent-proprietor's name.

According to the decision of the Enlarged Board of Appeal G 1/12 of 30 April 2014, which confirmed the existing jurisprudence, in order for an appeal to be

admissible, the appellant must be identifiable at the latest by the end of the 2-month time limit provided for in Article 108, first sentence EPC. This is the case if it is possible to derive from the information in the appeal with a sufficient degree of probability, where necessary with the help of other information on file, e.g. as they appear in the impugned decision, by whom the appeal should be considered to have been filed (point 26 of the reasons).
In the notice of appeal, the patent and the patent proprietor, as well as the decision which is impugned is identified and revocation of the patent is requested. The letter was filed by the representative having represented opponent 01 in the opposition procedure. From this it is sufficiently clear that the notice of appeal was filed on behalf of opponent 01 and thus the appeal is admissible.

3. *Main request - Article 123(3) EPC*

The subject-matter of claim 1 of auxiliary request 1 filed during oral proceedings before the opposition division, which is now the main request, had been amended by the addition of the following feature originating from the description:
"*where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have an average particle size of less than about 1000 nm*".

This feature has been introduced in claim 1 during opposition proceedings in order to further define the effective average particle size claimed in claim 1. It does not constitute a feature which has to be read independently from the other features of claim 1, but can only be seen as a further restriction as regards

said effective average particle size. The subject-matter of claim 1 can thus only be understood in that the "*effective average particle of the particles size (is) less than* about 1000 nm" **and** that "*at least 95% of the particles, by weight, have an average particle size of less than about 1000 nm*".

The appellants were right in saying that some particles may have a size larger than 1000 nm, but this was anyway the case even in the absence of the introduced term, since the particles were defined only by an effective average particle size of less than 1000 nm, thus potentially close from the claimed limit.

Thus, there is no broadening of the subject-matter of claim 1, and the main request meets the requirements of Article 123(3) EPC.

4. *Main Request - Article 123(2) EPC*

The feature "*where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have an average particle size of less than about 1000 nm*" originates from the original description, on page 19, lines 25-32, with the consecutive term "*when measured by the above-noted techniques*" omitted.
The referred passage previously mentions that "*particle size is determined on the basis of the average particle size as measured by conventional techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation*".
The reference by the term "*when measured by the above-noted techniques*" is thus made to any conventional technique for determining the average particle size,

and not exclusively to the three specific techniques specified in the same sentence. It is thus not necessary to complete the amended feature by the three specific methods of measurement.
In view of the broad nature of the term "*as measured by conventional methods*" there is no need to add this feature to the subject-matter of claim 1, which scope would remain unchanged.

The main request meets the requirements of Article 123(2) EPC.

5. Main Request - Article 100(b) EPC

5.1 The claimed invention refers to a nano-particulate composition having *"an effective average particle size of less than about 1000 nm, where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm"*.

Sufficiency of disclosure has been objected to by the appellants as regards the method of measurement of the particle size. According to the appellants, the person skilled in the art is not enabled by the disclosure of the patent to determine correctly the average particle size.

The description mentions in paragraph [0078] that "*particle size is determined on the basis of the average particle size as measured by conventional techniques well known to those skilled in the art, such as sedimentation field flow fractionation, photon correlation spectroscopy, or disk centrifugation*". The passage mentions specifically the Z-average particle

diameter measured by photon correlation spectroscopy (PCS).
Moreover, the measurements of the average particle size of particles, whatever the type of average value it might be, and even more of the weight particle size, are common measurements for the skilled person, who finds not only in the cited passage of the description but also from the common general knowledge sufficient information on how to measure any of said parameters.
There is thus sufficient disclosure as regards the parameters of average particle size, particle size by weight and their respective measurements.

5.2 Further arguments from the appellants

According to the appellants, different methods of measurement of the average particle size give rise to different results, and the method chosen has a significant influence on the final result achieved.

The Board agrees with the appellants. However, this point has no impact on sufficiency of disclosure, but rather on the uncertainty of what is covered by the subject-matter of independent claim 1, mainly limited by a parameter, namely "*the effective average particle size*".
It is true that in the art several types of *"average particle size"* and corresponding standardised test methods for determining them exist. It can be for instance a volume based particle size or a weight based particle size.
There is no doubt that variations occur according to the type of particle size as well according to the method of measurement chosen. Hence, the problem to be considered here boils down to the fact that, depending on the method of measurement, there exists an

uncertainty as to the actual claimed value for "*the effective average particle size*" mentioned in claim 1. This problem remains the same, however, even if a specific method of measurement was disclosed in the description since the claims would not be restricted to that method.
For these reasons, the Board takes the view that under the present circumstances the question of whether a skilled person can know what is covered by the claims is a question of definition of the claimed subject-matter, hence Article 84 EPC, rather than of sufficiency of disclosure (Article 83 EPC).

6. *Main request - Article 84 EPC*

The feature *"an effective average particle size of less than about 1000 nm"* was present in claim 1 as granted. During the opposition procedure, this feature was further completed and restricted by the term "*where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm*".

In claim 1 as granted, the nano-particulates were thus defined by their *"effective average particle size"*, without any specification of the type of average size and any method of measurement of said effective average particle size in the claims.
The absence of specification of type of average particle size led to uncertainty and unclarity as to the actual claimed value for "*the effective average particle size*" mentioned in claim 1.
Consequently, the problem of clarity linked with the measurement of the effective average particle size was already present in the claims as granted.

So was also the presence of the term *of "less than about 1000 nm"*.

In opposition, objections under Article 84 EPC may only be raised if they arise in relation to the amendments made, when said amendments do not derive from claims contained in the patent as granted. In present case, all unclear features were present in the claims as granted. Therefore, the objection to the clarity of the claim cannot be allowed.

As regards the term "*at least 95% of the particles, by weight, have a particle size of...*", there is no problem of clarity linked therewith. The size by weight is indeed a common parameter measurable by common techniques.

7. *Main Request - Novelty*

Examples 1 to 4 on pages 19 and 20 of document (1) refer to the preferred nano-particulate compositions comprising as active agent the *"Compound A"*. The description mentions further on page 21 the preferred active compound of the invention, which is different from aprepitant.
It is impossible to establish a relationship with the disclosure of the examples 4-11 with the list of active agents of pages 4 and 5 of the description of document (1), among which aprepitant was named (see page 4, lines 25-26). Especially more, since aprepitant was not cited as a particularly preferred compound, which list is given on pages 7 and 8 of the description.
This document does therefore not disclose directly and unambiguously a nano-particulate composition of aprepitant.

The subject-matter of the main request is novel over document (1).

8. Main request – Inventive step

8.1 The claimed invention relates to pharmaceutical compositions of 2- (R)- (1- (R)- (3, 5bis (trifluoromethyl)-phenyl) ethoxy)-3- (S)- (4-fluoro) phenyl-4- (3- (5-oxo-1H, 4H-1,2, 4triazolo) methyl-morpholine, thus aprepitant. The pharmaceutical compositions of this invention are useful in the treatment or prevention of disorders which benefit from the use of a tachykinin receptor antagonist, including central nervous system disorders such as psychiatric disorders including depression and anxiety, inflammatory diseases and emesis. The pharmaceutical compositions of the invention are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer; and in the treatment of post-operative nausea and vomiting (see par. [0135]). These pharmaceutical compositions have advantages over the other known pharmaceutical compositions of aprepitant in terms of increased oral bioavailability (see par. [0006], [0011], [0047]).

8.2 Document (3) relates to the preparation of a family of compounds useful for the prevention or treatment of nausea or emesis. It discloses in example 75 the preparation of aprepitant, and claim 1 of document (3) specifically refers to a method for the prevention or treatment of nausea or emesis induced by radiation or by cancer chemotherapeutic agents by administering aprepitant.
This document does not disclose any composition comprising aprepitant, but mentions a great number of

pharmaceutical compositions and excipients which can be used for the family of compounds (see col. 53-54). In particular, document (3) does not disclose a nano-particulate composition of aprepitant having absorbed on its surface a surface stabilizer.

This document constitutes the closest prior art, as agreed by the parties.

8.3 According to the patent, the problem of the claimed invention is the provision of a composition of aprepitant having increased bioavailability.

8.4 The proposed solution to this problem is a nano-particulate composition of aprepitant according to claim 1 having adsorbed on its surface thereof at least one surface stabilizer in an amount sufficient to maintain an effective average particle size of less than about 1000 nm, where "effective average particle size of less than about 1000 nm" means that at least 95% of the particles, by weight, have a particle size of less than about 1000 nm".

8.5 Given that no example of the contested patent showed experimental results, and in order to prove the existence of an effect, the respondent provided document (14).

8.5.1 Document (14) is a post-published journal publication relating to a nanoparticle formulation of MK-0869, namely aprepitant. The document compares the bioavailability of milled compositions of aprepitant, of respective mean particle sizes of 5.49 µm, 1.80 µm and 0.48 µm with a colloidal NanoCrystal® dispersion of aprepitant with mean particle size of 0.12 µm (see point 2.3.1). The colloidal NanoCrystal® dispersion was

prepared by a ball milling process of aprepitant in presence of hydroxypropyl cellulose, sodium dodecyl sulfate and sucrose (see point 2.2), providing thus the absorption of the excipients on the surface of aprepitant particles.
Table 1, Figures 2 and 3 of document (14) demonstrate a significant increase of bioavailability and a minimum impact of food on this bioavailability, as shown by the significantly higher values of the AUC obtained with the colloidal NanoCrystal® dispersion of aprepitant in comparison to the AUC values obtained by the other dispersions, and the absence of statistical difference in the AUC values obtained with on fasted or fed dogs treated with the colloidal NanoCrystal® dispersion.
The data provided by document (14) provide a strong confirmation that the absorption of aprepitant is dissolution rate-limited, and said absorption can be significantly increased by this specific nano-particulate composition (see point t 3.2).

Consequently, document (14) succeeds in showing that the claimed compositions have an increased bioavailability and the problem has been credibly solved.

As regards the food effect, document (14) indeed shows that food had a minimal impact on bioavailability in view of the absence of statistical difference in the AUC values obtained on fasted or fed dogs treated with the colloidal NanoCrystal® dispersion and shown in Table 1. Although not mentioned in the contested patent, this food effect is undoubtedly linked with increase of bioavailability. It is however not necessary to consider it in view of the effect observed on the bioavailability.

8.5.2 Further arguments from the appellants

According to appellant 02, it is not appropriate to rely on post published evidence to support an alleged technical effect.
The improvement of the bioavailability of aprepitant is only an alleged advantage merely referred to in the description of the contested patent, and is not properly supported by any evidence.
Moreover, document (14) mentioned that a key factor could affect the rate of dissolution of the nano-particulate formulation, namely the effectiveness of re-dispersion of the nanoparticles form a solid dosage form into the gastro-intestinal fluid (see docuemnt (14), par. 3.4).

The Board could not follow these arguments.
It is true that the improvement of the bioavailability is not supported by evidence in the description of the contested patent. The contested patent provides however a constant disclosure as regards the paramount necessity to improve said bioavailability of aprepitant and the corresponding benefits provided by the claimed composition (see paragraphs [0006],[0011] and [0047]). This necessity is seen as the main teaching of the contested patent.
As the improvement of bioavailability is derivable from the patent, any evidence can be taken into account to back up this information and to show an improvement over the prior art. It is thus appropriate to take into account post-published evidence submitted for the purpose of assessing whether or not the effect identified is indeed observed over the prior art. The provision of further technical teaching to support comparison with the closet prior art is even necessary and required to overcome the lack of support of the

alleged advantage, and demonstrate an inventive step on the basis of an improved effect.

As regards the possible factor that could affect the increase of bioavailability of the compositions disclosed in document (14), said document provides a solution to this potential drawback, namely the adaptation of the quantities of particular excipients, namely re-dispersing agents such as sucrose (see par. 3.4). The skilled person is therefore able to adapt the formulation so that the intrinsic properties of the naoparticlaute formulation of aprepitant are conserved.

8.6 It remains to determine whether the proposed solution is obvious.

Documents (5) and (6) disclose the preparation of nanoparticulate compositions of drugs with surface stabilizers adsorbed to their surface (see document (5) claim 1, col 1, lines 49-60; see document (6), page 2, lines 12-23 and 50-55 and claim 1). The documents mention that the dissolution-rate limited bioavailability of the drug is improved by said nano-particulate compositions.
Document (7) discloses the same type of nano-particulate compositions with surface stabilizers adsorbed to their surface for NSAID drugs.
These documents do thus not mention aprepitant as possible application of their teaching, although they give long lists of active agents, among pharmacological classes of drugs, such as anti-emetics agents, are mentioned in documents (5) or (6).

The skilled person would however not have applied the solution known from documents (5), (6) or (7) to aprepitant.

(a) The mention in documents (5) and (6) of therapeutic classes of drugs to which the teaching of these documents can apply, cannot serve as a link to a specific drug defined structurally, such as aprepitant. The problem of bioavailability is indeed not linked with the pharmacological activity of the drug, but rather with the intrinsic property of the drug. A generalisation of the properties of a drug to a whole therapeutic class, such as the anti-emetics, is not possible. As to the disclosure of document (7), it applies to a category of acidic drugs having different physico-chemical properties as aprepitant.

(b) As mentioned in document (14), low oral bioavailability of a drug can be attributed to several factors, such as slow dissolution rate, poor solubility, first-pass metabolism, chemical instability in the gastrointestinal tract, efflux transport, and poor permeability across the intestinal mucosa (see page 136, right-hand column). Different solutions exist for each of these factors to remedy the poor bioavailability of said drug.

As regards the improvement of low oral bioavailability specifically linked with a poor solubility of the drug, several solutions again exist to remedy it, such as the use of alternative salts, particle size reduction and amorphous dispersion, specific complexation with cyclodextrins, addition of surfactants or of lipid-based excipients (see document (14), page 137, left-hand column).

Thus, document (4), which states that aprepitant is a sparingly soluble drug, offers, as a solution to improve its bioavailability, the preparation of

a more soluble pro-drug derivate of aprepitant (see document (4) page 1234, right-hand col.).

(c) Moreover, an important prerequisite for using the milling technique used in present invention to obtain the claimed compositions, is that the drug, here aprepitant, has to be chemically and physically stable in the presence of excipients and under stressed conditions (see document (14), page 137, left-hand column, last par.).

It results that the skilled person, looking for a solution to the problem as defined above, faces multiple possible solutions to said problem of low bioavailability of aprepitant, and would not be conducted by the teaching of documents (5), (6) or (7) to the use of a nano-particulate composition of aprepitant having adsorbed on its surface thereof at least one surface stabilizer in an amount sufficient to maintain an effective average particle size of less than about 1000 nm .

Consequently, the main request meets the requirements of Article 56 EPC.

9. Reimbursement of the appeal fee

The appellants requested reimbursement of the appeal fee because the opposition division, in the oral proceedings, did not admit the objection under Article 123(3) EPC, because it was late filed and *prima facie* not relevant without giving any reasons in the decision for it.

According to Rule 103(1)(a) EPC, an appeal can only be reimbursed if the appeal is allowable. Since this is

not the case, as set out above, the requests for reimbursement of the appeal fee are to be rejected.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

S. Fabiani J. Riolo

Decision electronically authenticated