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Datasheet for the decision of 7 July 2025

Case Number: T 1847/23 - 3.3.07

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Language of the proceedings: EN

Title of invention:
MAROPITANT FORMULATION

Patent Proprietor:
Le Vet B.V.

Opponents:
Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB
Krka, d.d., Novo mesto

Headword:
Maropitant/LE VET

Relevant legal provisions:
EPC Art. 54, 56, 84

Keyword:
Main request - Novel and Inventive (Yes)
Main request - Clarity (Yes)

Decisions cited:
G 0002/21

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Case Number: T 1847/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 7 July 2025

Appellant: (Opponent 1)	Hoffmann Eitle Patent- und Rechtsanwälte Partnerschaftsgesellschaft mbB Arabellastr. 30 81925 München (DE)
Appellant: (Opponent 2)	Krka, d.d., Novo mesto Smarjeska cesta 6 8000 Novo mesto (SI)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Le Vet B.V. Wilgenweg 7 3421 TV Oudewater (NL)
Representative:	Mewburn Ellis LLP Aurora Building Counterslip Bristol BS1 6BX (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 4 October 2023 concerning maintenance of the European Patent No. 3173071 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	D. Boulois
	Y. Podbielski

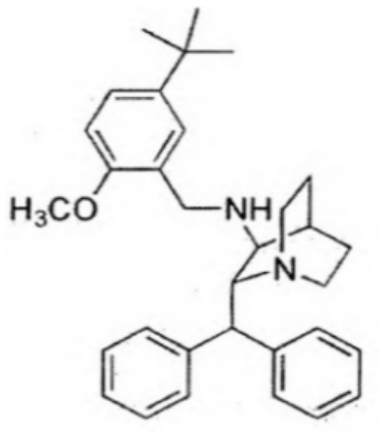
Summary of Facts and Submissions

I. European patent 3 173 017 B1 had been opposed under Article 100 (a), (b) and (c) EPC on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

II. The appeals lie from the decision of the opposition division finding that the patent in amended form meets the requirements of the EPC. The decision was based on the main request filed on 27 April 2023.

Independent claim 1 of the main request read as follows:

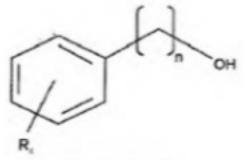
"1. Pharmaceutical composition comprising: an aqueous solution of:
a) maropitant citrate, the maropitant having the structural formula I:



Formula I

b) a pharmaceutically acceptable ß-cyclodextrin,

c) 7-18 mg/ml of a pharmaceutically acceptable preservative according to formula II:



Formula II

wherein R_x is selected from the group consisting of hydrogen, C_1-C_5 hydrocarbyl, heteroatom or halogen substituted C_1-C_5 hydrocarbyl, halogens and heteroatoms, x being an integer between 1 and 5, n being an integer between 1 and 4,

wherein the pharmaceutically acceptable preservative is phenylmethanol."

III. The documents cited during the opposition proceedings were the following:

Annex HE1

D1: WO 2005/082416 A2
D2: WO 2013/078500 A1
D5: Meyer et al., Journal of Pharmaceutical Sciences, 96(12): 3155-3167, December 2007
D6: EMEA "Note for Guidance on Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products", CPMP/CVMP/QWP/115/95, 8 July 1997
D7: Kappelgaard et al., Hormone Research, 2004, 62 (Supplement 3): 98-103
D8: Deckers et al., Veterinary Record Open, 2018, 5:e000262 4.

D9: Broadhead & Gibson, Chapter “Parenteral Dosage Forms” in “Pharmaceutical Preformulation and Formulation”, CRC press, 2nd edition 2009
D11: Strazar & Lalonde, CMAJ 2012, 184(18), p. 2016
D12: Merola & Mills, J Feline Med Surg, 2016 Feb, 18(2), p. 60-76
D13: Williams & Howe, J Dermatologic Surgery Oncol., 1994, Vol. 20 (11), p.730-733
D14: St Peter et al., Am J Kidney Dis, 1998, Vol. 32 (3), p. 470-474
D15: Wilson & Martin, Ann Emerg Med, 1999, Vol. 33 (5), p. 495-499
D16: Belliveau & Jordan, CMAJ (2012), 184(15), p. 1715 “Minimizing injection pain”
D17: Yuen & Dolman, Ophthal Plast Reconstr Surg 1999, 15, No. 2, p. 143-147
D18: Rasmussen et al., Helv Paediat Acta, 1988, 43, p. 443-448
D19: CN103637987A (English translation via Patent Translate)
D21: EP 1 800 689 A1
D22: J P 63-40166
D23 Machine translation of JP 63-40166 (D22)
D26: "Solubilization of Synthetic Perfumes by Nonionic Surfactants and by Sulfoalkyl Ether ß-CDs" by Q. Qu et al., Journal of Inclusion Phenomena and Macrocyclic Chemistry 45, 2003, 83-89
D31: Denyer & Wallhaeusser, Chapter 11: Antimicrobial Preservatives and Their Properties; In: Denyer & Baird, 1990, Guide to microbiological control in pharmaceuticals; Denver, CO: CRC Press
D32: Griffenhagen et al., Veterinary Anaesthesia and Analgesia, 2015 (42):472-483
D38: M.H. Court “Feline drug metabolism and disposition: pharmacokinetic evidence for species differences and molecular mechanisms” in Vet Clin North

Am Small Anim Pract. 2013 September; 43(5):. doi: 10.1016/j.cvsm.2O13.05.002
D39: EMA "Specifications and control testing of the finished product".

IV. According to the decision under appeal, the subject-matter of claim 1 of the main request met the requirements of Article 84 EPC.

The subject-matter of claim 1 of the main request met the requirements of Article 123(2) EPC, specifically concerning the feature "7-18 mg/ml phenylmethanol".

The requirements of Article 83 EPC were also met and the subject-matter of claim 1 was novel over D1.

With regard to inventive step, the closest prior art was D1 and claim 1 of the main request differed from the closest prior art in the concentration of benzyl alcohol which ranged from 7-18 mg/ml contrary to the concentration of 2% in table III on page 28 in D1 which equalled 20 mg/ml. The technical information in Annex 3 was taken in account, since the problem of stability was a common technical problem in the technical field of pharmaceutical compositions comprising active pharmaceutical compounds. Consequently, the technical problem over D1 was the provision of a composition comprising maropitant and cyclodextrin suitable for administration to veterinary animals having improved stability. The opposition division considered that the problem was solved over the whole scope of the claim and was not obvious in view of D1, D6, D7, D9, D13, D16 and D30.

V. Opponent 01 (hereinafter appellant 01) and opponent 02, (hereinafter appellant 02) filed an appeal against said decision.

VI. With its statement setting out the grounds of appeal dated 2 February 2024, appellant 02 submitted the following item of evidence:

Annex HE2

VII. With its reply to the statement of grounds of appeal dated 19 June 2024, the patent proprietor (hereinafter the respondent) filed the following requests:
- a main request corresponding to the request maintained by the opposition division
- AR0a, AR0b, AR0c;
- ARs 1-15 and the corresponding versions a, b and c.

The respondent submitted also the following piece of evidence:

Annex 3 - Stability tests (already filed during the opposition proceedings on 27 May 2022).

VIII. A communication from the Board, dated 9 April 2025, was sent to the parties.

IX. Oral proceedings took place on 7 July 2025.

X. The arguments of the appellants may be summarised as follows:

Main request - Novelty

Appellant 01 argued that it was possible to combine the teaching of Table III with the disclosure of the general section of D1.

Appellant 02 considered that the statement on page 27, lines 17-18 of D1, i.e. that "each antimicrobial preservative was tested at the highest concentration currently used in commercial products", should have been interpreted as an indication that within the broad range of 0.1-600 mg/ml, only those sub-ranges are relevant for a specific preservative of interest, which should not exceed the highest concentrations of Table III. This would have been be the sub-range of 0.1-20 mg/ml in view of the common general knowledge disclosed in D6.

The phenylmethanol embodiment in table III of D1 as starting point for the assessment of inventive step

According to appellant 01, there was no effect shown over this disclosure. The effect on stability shown in Annex 3 should not be considered in view of decision G 2/21, and considering that said effect was in any case not convincingly shown, in particular in view of the experiments of Annex HE1. The effects shown in Annex 3 were furthermore not related to stability. The technical problem could only be the provision of an alternative composition. The solution was obvious since it was known that benzyl alcohol decreased the injection pain. D13, D14, D15, D18 or D7 were the relevant documents in this regard.

Appellant 02 also considered that the stability effect of Annex 3 was not derivable from the teaching of the

application and that it could not be considered in view of decision G 2/21. The problem had to be defined as the provision of an alternative composition and the solution was obvious in view of *inter alia* D5, D6 or D38.

The meta-cresol embodiment of D1 as starting point for the assessment of inventive step

During the oral proceedings the appellants defined the problem over this disclosure as the provision of a composition with improved site tolerance. The claimed solution was obvious since benzyl alcohol was known as local anaesthetic, and was known to be more active than meta-cresol. Documents D7, D2, D18 and D26 were cited in this regard.

Main request - Article 84 EPC

The subject-matter of claim 1 has been objected to by appellant 01 in view of formula II which has been introduced during the opposition proceedings. According to appellant 01, claim 1 suffers from a lack of clarity in view of the term "heteroatom" relating to the possible meaning for R_x and of the wording "heteroatom...substituted C_1-C_5"; appellant 01 argues that it is not clear which atom qualifies as "heteroatom", and that the wording "heteroatom...substituted C_1-C_5" does not make clear which of these groups is bonded to the remainder of the molecule.

Appellant 02 considers that the terms "heteroatom" and "an integer between 1 and 5" in the definition of R_x are unclear, since they lead to confusion as to which preservatives would fall under formula II. Appellant 02

also considers that the addition of formula II in claim 1 contravenes Article 84 EPC as this amendment does not clearly establish that the pharmaceutical composition is indeed limited to 7-18 mg/ml of any preservative according to formula II, as part (c) further requires that the preservative is phenylmethanol.

The appellants consider that the meaning and scope of formula II is crucial for determining the preservative compounds, for which said amount limitation is effective.

XI. The arguments of the respondent may be summarised as follows:

Main request - Novelty

The skilled person would not have combined different embodiments within D1. D1 focused on meta-cresol whereas phenylmethanol (benzyl phenol) was not investigated in the experimental section.

The phenylmethanol embodiment in table III of D1 as starting point for the assessment of inventive step

Stability was part of the invention and was derivable from the application as filed, and the improvement of stability had to be taken in account. The claimed solution was inventive.

D1 taught away from the inclusion of phenylmethanol as a preservative rather than m-cresol, as the experimental section emphasised the excellent stability and injection site tolerance of m-cresol (see p. 36, lines 4-6) and performed long term stability studies on

m-cresol compositions. No such studies were performed on phenylmethanol-containing compositions.

None of the other documents cited bridged the gap between the disclosure of D1 and present claim 1. The skilled person would clearly consider documents relating to injection site tolerance in animals to be different to those relating to studies carried out in human patient groups, due to differences in pain perception between humans and veterinary animals.

The meta-cresol embodiment of D1 as starting point for the assessment of inventive step

There was no secondary document to D1 which could have given a reasonable expectation of success, with regard to the use of benzyl alcohol and its claimed concentration range. In particular, there was no cyclodextrin in the compositions disclosed in D7 or D18, and the drug was different.

XII. Requests

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

The respondent (patent proprietor) requested that the appeal be dismissed and that the patent thus be maintained in the version held allowable by the opposition division (main request), alternatively if the decision under appeal is set aside that the patent be maintained on the basis of one of the following auxiliary requests filed with its reply dated 19 June 2024, in the order given in the Table on pages 34-36 of that reply:

- AR0a, AR0b, AR0c,
- AR1-15 and the corresponding versions a, b and c.

Reasons for the Decision

1. Main request - Novelty

1.1 Novelty was objected to by the appellants in view of the disclosure of D1 on page 27, line 14 to page 28, line 11, including Table III, and the general teaching on page 4, lines 21-22.

1.2 D1 relates to the preparation of formulations comprising maropitant, a ß-cyclodextrin and a preservative.

This document discloses on page 28 the preparation of preserved formulations comprising maropitant citrate and 5% or 10% (weight/volume) of β-cyclodextrin (see page 28, lines 5-11). Several preservatives were screened and added to the formulation on a weight basis as shown in Table III:

Table III: Antimicrobial Preservatives Screened

Antimicrobial preservative	Percent (w/v)	pH
Phenol	0.5%	4.4
meta-cresol	0.3%	4.4
meta-cresol + EDTA	0.5% meta-cresol + 0.15% edta	4.4
Chlorocresol	0.1%	4.4
Chlorocresol + EDTA	0.1% + 0.15% edta	4.4
Chlorobutanol	0.5%	3.5
Chlorobutanol & Phenylethanol	0.5% each	3.5
Chlorobutanol & Phenylethanol	0.5% Chlorbutanol w/ Titration of Phenylethanol**	3.5
Phenylethanol	0.5%	3.5
Thimerosal	0.01%	4.4
Benzoic Acid	0.2%	3.5
Benzethonium chloride	0.02%	4.4
Benzalkonium chloride	0.01%	4.4
Benzyl alcohol	2.0%	4.4
Propylene glycol	25%	4.4
Ethanol	15%	4.4
Bronopol	0.1%	5.0
Sucrose	50%	4.4
Chlorhexidine gluconate	0.5%	5.0

** Titration of Phenylethanol from 0.5-0.1% in 0.1% increments

One of the disclosed option is the addition of **2 % w/v benzyl alcohol, i.e. 20 mg/ml of phenylmethanol**, at pH 4.4 as an antimicrobial preservative (see Table III). **The concentration of benzyl alcohol is therefore outside of the claimed range of 7-18 mg/ml. Accordingly, this disclosure cannot be novelty-destroying.**

The further passages on which the opponents rely do not mention benzyl alcohol and/or the claimed range of 7-18 mg/mL and are therefore not relevant:
- the description on page 27, lines 15-20 mentions that "Table III summarizes the antimicrobial preservatives evaluated for use in the formulation. Each antimicrobial preservative was tested at the highest concentration currently used in commercial products.";
- the general disclosure on page 4, lines 21-22 states that "preferably, the concentration of preservative is about 0.1 mg/mL to about 600 mg/mL. Preferably, the preservative is meta-cresol and is in a concentration of about 0.1 mg/ml to about 20mg/ml". This concentration range of 0.1 mg/ml to 600 mg/ml is also

disclosed in preferred embodiment E on page 37, lines 18-19.

1.3 In relation to these passages of D1, the Board concurs with the conclusion of the opposition division regarding novelty, i.e. that the subject-matter of claim 1 is novel over D1, since D1 does not disclose directly and unambiguously a composition comprising maropitant citrate, β-cyclodextrin, and **in particular benzyl alcohol/phenylmethanol in a concentration of 7 to 18 mg/ml.**

1.4 The Board does in particular not follow the appellants' line of argument regarding novelty, which consisted in the combination of the disclosure of Table III with the further cited passages of the description of D1, namely on pages 27 or 4, or even with a further document, namely D6, which mentions the range of 0.1-20 mg/ml for benzyl alcohol as the usual range of use.

As a general principle, the content of a prior art document cannot be treated as a reservoir from which it would be permissible to draw features belonging to distinct embodiments to artificially create a particular novelty-destroying embodiment, unless the document itself unambiguously supports such a combination; the same conclusion applies with the citation of a further document in association with the disclosure of the prior art document.

This applies to the present case, since there is no indication of combining the specific features of Table III with any alternative concentration or range of concentrations of a preservative disclosed in another part of the description. The mention on page 27 that the disclosed concentrations of Table III are the

highest concentration currently used in commercial products can in particular not be seen or understood as an invitation to substitute the concentration values given in Table III.

1.5 Consequently, the main request meets the requirements of Article 54 EPC.

2. Main request - Inventive step

2.1 The claimed invention relates to a pharmaceutical composition comprising maropitant, cyclodextrin, and a preservative. The composition has an improved injection site tolerance when injected to animals such as cats or dogs, and also meets the Pharmacopeias antimicrobial requirements (see the specification, par. [0012]-[0015]).

2.2 The closest prior art is D1 which relates to pharmaceutical compositions comprising maropitant. The purpose of the invention of D1 is to improve the injection site toleration of injectable aqueous solutions comprising maropitant, a cyclodextrin and a preservative (see D1, page 2, lines 1-5).

Benzyl alcohol, i.e. phenylmethanol, is mentioned twice as preservative in the whole disclosure of D1:
- On page 12, lines 19-34, D1 states that a preliminary screen for an antimicrobial preservative is conducted and includes *inter alia* benzyl alcohol in a list of preservatives, but does not give any conclusion with regard to the use of benzyl alcohol (see also Tables VII and VIII). There is furthermore no disclosure in D1 on any experiment regarding the injection site tolerance with a composition comprising benzyl alcohol.

- Table III (page 28) discloses *inter alia* a formulation comprising 10 mg/ml maropitant citrate, 5-10% of SBE-CD and 2% by weight of benzyl alcohol at pH 4.4 (see also point 1.2 above); the efficacy of the formulation comprising benzyl alcohol is **not** tested in D1. In Table III, several other examples of compositions comprising meta-cresol or alternative preservatives are disclosed with the same amounts of maropitant citrate and SBE-CD.

Based on the overall disclosure of D1, it is evident that this document primarily pertains to the use of meta-cresol, or to a lesser degree to thimerosal, propylene glycol or phenol as preservative for compositions comprising maropitant and cyclodextrin (see D1, for instance page 4, lines 19-23, page 37, lines 12-14 or claim 4). The examples of D1 teach for instance that, in order to improve injection site tolerance of a composition comprising maropitant and cyclodextrin and to have acceptable storage stability, **the most preferable preservative to be used is meta-cresol** (see D1, page 12, lines 26-28; page 30, "Injection Site Toleration"; page 36, lines 3-9).

Consequently, the disclosure of D1 presents several aspects which can constitute the starting point for assessing inventive step, namely the meta-cresol embodiment in D1 or the phenlymethanol embodiment in Table III of D1.

In its decision, the opposition division took as starting point for the assessment of inventive step the disclosure of D1 relating to phenylmethanol, namely the composition disclosed in Table III. The Board will first make a review of the decision of the opposition

division, and the validity of the decision will be first examined in relation to this disclosure.

2.3 The phenylmethanol embodiment in Table III of D1 as starting point for the assessment of inventive step

2.3.1 Claim 1 of the main request differs from this disclosure of D1 in the presence and the concentration of benzyl alcohol which ranges from 7-18 mg/ml contrary to the concentration of 2% in Table III on page 28 in D1 which equals 20 mg/ml.

2.3.2 The opposition division considered in its decision that the problem over this embodiment of D1 is the provision of a composition comprising maropitant and cyclodextrin which is suitable for administration to veterinary animals having **improved stability**.

Appellants 01 and 02 define respectively the problem as the provision of **an alternative maropitant formulation** and the provision of **an alternative maropitant containing pharmaceutical composition** for administration by injection.

The respondent gives several definitions of the problem:

(a) if **the experiments of Annex 3 are taken in account**, the problem is the provision of a composition comprising maropitant and cyclodextrin suitable for administration to veterinary animals **which has improved stability**;

(b) if t**he experiments of Annex 3 are not taken in account**, the problem is the provision of **an alternative composition** comprising maropitant suitable for administration to veterinary animals which leads to a low level of pain on injection.

2.3.3 Hence, Annex 3 was discussed in support of a technical effect with regard to stability at low temperatures, while examples 5 and 6 of the patent were also mentioned in the written proceedings.

(a) Examples 5 and 6 show the efficacy of phenylmethanol with regard to injection site tolerance, and show an improvement over compositions comprising m-cresol or phenyl ethanol as preservative. The examples do however not provide a comparison with a composition comprising 20 mg/mL of benzyl alcohol as disclosed in D1.

(b) Annex 3 presents a set of experiments referred to as "Stability tests", wherein a composition according to the invention containing 11.1 mg/mL of benzyl alcohol, is compared to an identical composition containing 20 mg/mL of benzyl alcohol.

The tests were performed as several thermal cycles, i.e. three cycles, comprising a freeze cycle at -18°C for a minimum of 24 hours, followed by a thaw cycle at room temperature (15 to 25°C) for at least 24 hours.

The tests show that, prior to filtration, the 20 mg/mL composition was a non homogenous solution or emulsion, with visible oily droplets, while the 11.1 mg/mL composition was a clear and colourless to light yellow solution; after filtration the 20 mg/mL composition became however clear and colourless. The same was observed after respectively 1, 2 and 3 freeze/thaw cycles, i.e that the 20 mg/mL composition was coloured; however

no filtration was performed after the freeze/ thaw cycle.

Annex 3 concludes that the 11.1 mg/mL composition was more stable; the oily droplets contained a higher amount of maropitant than the solution, meaning that it was difficult to control the concentration of maropitant in a given sample for injection, and may lead to a higher dose of unbound maropitant injected into the animal, which may lead to increased pain.

2.3.4 The opposition division considered that the technical information provided by Annex 3 had to be taken into account for the assessment of an allegedly unexpected effect. In its decision, the opposition division explained that it was convinced that the problem of stability is a common technical problem in the technical field of pharmaceutical compositions comprising an active pharmaceutical compounds. This view is also shared by the respondent. The Board however disagrees with this conclusion.

According to decision G 2/21, it is possible to rely upon a technical effect for inventive step if the skilled person, having the common general knowledge in mind, and based on the application as originally filed, would derive said effect as being encompassed by the technical teaching and embodied by the same originally disclosed invention.

In the present case, the technical effect shown in Annex 3 is not derivable from the application. The reasons are the following:

(a) First, the application as filed does not contain any observation in relation to the stability of

the claimed compositions, even less at specific low or very low temperatures or after freeze/ thaw cycles; none of theses aspects are mentioned or derivable from the original application.
As pointed out by the opponents, it is also debatable whether the tests conducted by the patent proprietor can be classified as 'stability tests.' The experiments merely reveal a transient behavior of the compositions at low temperatures. The patent proprietor has not demonstrated that these experiments represent a commonly employed method for assessing the stability of such compositions.

Moreover, according to the description, benzyl alcohol is used as antimicrobial preservative and as agent for reducing the pain at injection. There is no indication that this substance could have an impact on the behaviour of the compositions at low temperatures.

There is also not any mention in the patent of a possible instability of the solution in the presence of higher concentrations of benzyl alcohol which appears furthermore to be contradicted by the results of Annex HE1 (see "Observations").

(b) Moreover, the preparation and/or storage of a drug composition at low or very low temperatures is neither systematic nor widely practiced. Indeed, there is no indication in the application as filed or in the prior art that the compositions comprising maropitant have to be prepared and/or stored under these conditions. Hence, the preparation and/or the storage at extremely low temperatures, as well as the behaviour of the claimed compositions at these temperatures does not

appear to constitute a property tipically sought by a person skilled confronted with the problem of preparing this class of compositions.

This is confirmed in particular by the teaching of other documents such as D10 which indicates that the maropitant injectable formulation is to be stored **at controlled room temperature** of 20 to 25°C (see D10, page 3), or D40 which recommends **to not freeze** the commercial injectable product comprising maropitant (see page 6).

Consequently, the behaviour of compositions comprising maropitant under low or very low temperatures **cannot be considered as a common problem** as argued by the opposition division in its decision.

In view of the above, the Board considers that the skilled person would not derive the effects considered in the experiments of Annex 3 as being encompassed by the technical teaching and embodied by the originally disclosed invention. Thus, these effects cannot be relied upon in light of decision G2/21.

2.3.5 Examples 5 and 6 of the contested patent show convincingly a good injection site tolerance and antimicrobial efficacy. Accordingly, the problem is **the provision of an alternative composition comprising maropitant suitable for administration to veterinary animals which leads to a low level of pain on injection.**

2.3.6 The claimed solution is an injectable composition of maropitant citrate comprising a concentration of benzyl alcohol ranging from 7-18 mg/ml.

2.3.7 Obviousness

In the Board's view, a crucial point for the assessment of inventive step in the present case is whether the teaching of D1 would provide an incentive to the skilled person to use phenymethanol, i.e. benzyl alcohol, in particular in a concentration range of 7-18 mg/mL in order to alleviate pain injection.

As already mentioned above under point 2.2, D1 relates essentially to the use of meta-cresol, or to a lesser degree to thimerosal, propylene glycol or phenol as preservative for compositions comprising maropitant and cyclodextrin. The examples of D1 teach that in order to improve injection site tolerance of a composition comprising maropitant and cyclodextrin and to have acceptable storage stability, the most promising preservative to be used is meta-cresol (see D1, page 12, lines 26-28; page 30, "Injection Site Toleration"; page 36, lines 3-9).

The teaching of D1 demonstrates that the use of benzyl alcohol as preservative and as pain relieving agent was not deemed suitable, and was ultimately dismissed. The preliminary screening for an antimicrobial preservative conducted in D1, which included benzyl alcohol as a potential candidate (see page 12), reveales that only thimerosal, chlorobutanol/phenylethanol, ethanol and propylene glycol satisfied the requirements of the USP/ Eur. Phamacopoeia; Tables VII and VIII on pages 33-35 do not even present any result regarding the antimicrobial effectiveness of benzyl alcohol, while the stability of seven different preservatives is tested. When considering the injection site tolerance, D1 identifies thimerosal and meta-cresol as effective

compounds on page 12 and concludes on page 36 that meta-cresol was identified as the preferable antimicrobial preservative due to its excellent injection site tolerability and preservative efficacy; there is again no mention of benzyl alcohol in the same passage.

Based on this teaching, the skilled person can only conclude that benzyl alcohol is not a suitable preservative agent for compositions comprising maropitant and cyclodextrin.

The Board agrees with the respondent that D1 only mentions phenylmethanol/benzyl alcohol in a single "paper" example and that a skilled person would not have considered an embodiment relating to phenylmethanol/benzyl alcohol to be a particularly suitable starting point for the development of the present invention. In the same context, the Board disagrees with the appellants that the citation of benzyl alcohol in D1 must be seen as an invitation to perform further tests. In contrast, as previously noted, page 12 of D1 (lines 19 to 25) reveals that a preliminary screen to identify an antimicrobial preservative was conducted with several preservative agents including benzyl alcohol. However, benzyl alcohol was ultimately not selected as one of the suitable preservative agents that satisfied the USP/Ph. Eur. requirements.

In addition and as argued by the respondent, it is not possible to find an incentive in D1 to use benzyl alcohol at the specific concentration range of 0.7-18 mg/mL. D1 mentions indeed that the cyclodextrin used to form the inclusion complex with maropitant may also bind preservatives; **this complexation with the**

preservative results in a decrease in antimicrobial effectiveness and acceptable injection site tolerance (see D1, page 2, lines 10-15). It is necessary to obtain an optimal balance between the concentration of maropitant, cyclodextrin and antimicrobial preservative. In view of this complexation, the effective concentration of benzyl alcohol for preservation and pain alleviation does not appear to be predictable; In the Board's view, assuming for the sake of argument that the skilled person would have considered to prepare a composition containing benzyl alcohol he would have then envisaged to use a concentration higher than the usual concentration for preservation, i.e. over 20 mg/mL (cf. D6) having regard that this concentration was not sufficient to provide an acceptale level of antimicrobial activity.

Accordingly, the claimed solution is inventive over D1 as closest prior art alone.

2.3.8 The claimed solution is not apparent from any of the further cited documents. Documents D2, D5-D9, D11-D12, D13-D18, D19, D21, D23, D31, D32, D38 and D39 have been cited by the parties in this context either during the oral proceedings or in the written proceedings. None of these documents can however provide a teaching which could render the solution obvious:

(a) It emerges from documents D5, D9, D21 or D31 that benzyl alcohol is one of the most commonly used preservatives, in particular at concentrations around 9-10 mg/ml (see D5, page 3156; D9, Table 2 on page 330; D21, Table 4.2; D31, page 265).

D2 and D19 disclose compositions comprising cyclodextrin and benzyl alcohol as preservative and

a drug different from maropitant(see D2, claims 4 and 5; see D19 paragraph [0079]); these documents do not disclose any effect on the injection site tolerance.

It was also known that benzyl alcohol is a pain relieving agent in particular in the case of parenteral administration, as illustrated by documents D7 (see page 101), D13 (see Abstract), D14 (see pages 470-471), D15 (see Tittle), D16 (See "Minimizing Injection Pain"), D17 (See Abstract), D18 (see Abstract), D23 (see Claim 1) or D33 (See Abstract).

These documents neither disclose the administration of pharmaceutical compositions to animals nor concern compositions comprising maropitant. Consequently, these document would not provide any relevant guidance to the skilled person confronted with the technical problem defined above.

(b) Among the cited documents, only D6, D12, D32 and D38 deal with the administration to animals, but do not relate to compositions comprising maropitant. None of these documents points to the use of benzyl alcohol for improving pain at the injection site, in the specific claimed concentration range, in combination with maropitant and cyclodextrin.

D6 mentions on page 6 that some antioxidants or antimicrobial preservatives may be undesirable under certain circumstances, e.g. benzyl alcohol when used in parenteral products for children under the age of 2 years or in newborn animals or in cats (see point 5.1).

D32 discloses the addition of 2% benzyl alcohol as preservative to a parenteral composition of propofol for cats. D32 mentions that cats are deficient in the glucuronidation pathways necessary for timely clearance of *inter alia* benzyl alcohol, and that benzyl alcohol is unlikely to cause any clinically relevant adverse effects when administered at this dose (see Discussion).

D38 mentions on page 7 that, in view of the possible toxic effects on cats, the amounts of benzyl alcohol must be minimized.

D7 mentions also experiments on rats on page 101. The results disclosed in this document suggest that the antimicrobial benefits of benzyl alcohol (9 mg/ml) when used as preservatives in drug formulations are not overshadowed by local irritation potential. These experiments appear to have been performed without any drug and without cyclodextrin and are not relevant for this reason.

Thus, none of the above documents addresses the challenge of developing a composition that incudes maropitant, cyclodextrin and a preservative agent.

2.3.9 Consequently, the subject-matter of claim 1 of the main request is inventive when starting from the phenylmethanol embodiment in Table III of D1.

2.4 The meta-cresol embodiment of D1 as starting point for the assessment of inventive step

2.4.1 Claim 1 of the main request differs from this disclosure of D1 in the presence and the concentration of benzyl alcohol which ranges from 7-18 mg/ml whereas

D1 discloses the use of meta-cresol in a concentration of 0.1 mg/mL to 20 mg/mL (see D1, page 4, lines 19-23 or page 37, lines 20-22).

2.4.2 The respondent defines the objective technical problem as the provision of a composition comprising maropitant and cyclodextrin suitable for administration to veterinary animals having improved injection site tolerance.

During the oral proceedings, the appellant provided the same definition of the problem.

2.4.3 Example 5 of the contested patent shows in its results of Tables 4 and 5 that formulations containing 10 mg/ml phenylmethanol (benzyl alcohol) lead to better injection site tolerance in cats than compositions comprising m-cresol as shown in Table 3.

Example 6 shows that compositions comprising 10 mg/mL phenylmethanol lead to a better injection site tolerance, than compositions comprising phenyl ethanol.

The results of examples 5 and 6 are also confirmed by the experimental results of the post-published document D8.

These experiments confirm that the problem is as defined by the respondent.

2.4.4 Obviousness

As explained under 2.3.7 above, the skilled person would not identify any incentive in D1 to substitute m-cresol by benzyl alcohol, since benzyl alcohol has been discarded in D1 as a suitable preservative agent for a

composition comprising maropitant and cyclodextrin. The citation of further documents has no impact on this finding.

In this context, documents D2, D7, D18, D23 and D26 were mentioned. Among these documents, only D7 and D18 mention a better efficacy of benzyl alcohol over m-cresol, but they are not relevant in the present context, since they do not disclose a composition with maropitant and/or cyclodextrin:

(a) D2 discloses compositions comprising a drug, cyclodextrin and benzyl alcohol (see D2, claims 4 and 5). Said document does however not disclose any effect on the injection site tolerance and does not relate to maropitant. Accordingly, the skilled person would not find any incentive in D2 towards the claimed solution.

(b) D23 discloses a parenteral composition of an active ingredient with benzyl alcohol as pain relieving agent; cyclodextrin is also included in the disclosed compositions for reducing the hemolytic action of benzyl alcohol. This document relates to a human study, with a different medication, and the amount of benzyl alcohol used (namely **2% or above**) is higher than that specified in present claim 1. Therefore, a skilled person attempting to solve the above defined objective technical problem, would not have been motivated to derive a composition according to present claim 1 from the combination of D1 and D23.

(c) D26 is a study on the solubilization of synthetic perfumes by non-ionic surfactants and by sulfoalkyl ether β-cyclodextrin. This document indicates that

in each surfactant solution studied, the partition coefficient with benzyl alcohol is the lowest. Appellant 02 argued that this showed that benzyl alcohol had not a great effect on the formation of a complex with cyclodextrin, and would not displace the complex drug-cyclodextrin. In the Board's view it is questionable whether the skilled person would consider this document at all given that it does not pertain to the pharmaceutical field. In any event, this document provides no information regarding the molecular interactions within a composition comprising, maropitant, cyclodextrin and a preservative agent. As explained in D1 (see sentence spanning pages 11 and 12) the effectiveness of the preservative agent is influenced by these interactions.

(d) It was demonstrated in D7 that pain perception of the injection of a composition of growth hormone to humans was similar between formulations containing phenol and benzyl alcohol, whereas m-cresol was associated with more painful injections than benzyl alcohol (see abstract).

(e) D18 reports that local discomfort at the injection site of a growth hormone composition disappeared after changing meta-cresol in the solvent to 0.9% benzyl alcohol (see abstract). This document relates to a human trial and does not relate to the drug maropitant or to a composition comprising cyclodextrin, and cannot be considered as relevant for this reason.

Consequently, none of these documents provide an incentive to use benzyl alcohol in a concentration of 7 to 18 mg/ml in a composition comprising maropitant and

cyclodextrin, instead of meta-cresol for improving the injection site tolerance in animals.

2.4.5 The subject-matter of claim 1 is thus also inventive when starting from the meta-cresol embodiment of D1 as starting point for the assessment of inventive step.

2.5 In view of these conclusions, the main request meets the requirements of Article 56 EPC.

3. Main request -Article 84 EPC

3.1 Claim 1 was objected to by the appellants in view of the term "heteroatom" relating to the possible meaning for R_x and of the wording "heteroatom...substituted C_1-C_5", and also since they lead to confusion as which preservatives would fall under formula II.

The appellants also consider that the addition of formula II in feature c) of claim 1 contravenes Article 84 EPC as this amendment does not clearly establish that the pharmaceutical composition is indeed limited to 7-18 mg/ml of any preservative according to formula II, as part (c) further requires that the preservative is phenylmethanol.

3.2 In the Board's view, the wording of feature c) of claim 1 serves to limit the presence of a preservative to specifically 7-18 mg/ml of phenylmethanol, while excluding the further presence of any further preservative of formula II. Its interpretation does not appear to be unclear.

3.3 The terms "heteroatom" relating to the possible meaning for R_x and the wording "heteroatom...substituted C_1-C_5" do not present any lack of clarity; there is no

necessity to consult the description to understand the term. The skilled person is indeed able to identify what is meant by the term "heteroatom", i.e. any atom that is not carbon or hydrogen, and how it can be linked to a C_1-C_5 radical. The term is broad, but broadness does not signify lack of clarity.

Accordingly, the Board considers that claim 1 clearly defines the meaning of R_x in formula II.

3.4 Consequently, the subject-matter of claim 1 is clear and the main request meets the requirements of Article 84 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated