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**Datasheet for the decision
of 13 September 2018**

Case Number: T 0740/14 - 3.3.01

Application Number: 05716238.0

Publication Number: 1778234

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A61K31/4427, A61K31/444,
A61K31/4166, A61P9/00

Language of the proceedings: EN

Title of invention:

PIMOBENDAN TO BE USED FOR THE REDUCTION OF HEART SIZE IN
MAMMALS SUFFERING FROM HEART FAILURE

Patent Proprietor:

Boehringer Ingelheim Vetmedica GmbH

Opponent:

VIRBAC

Relevant legal provisions:

EPC Art. 54(5), 83, 54(2), 56
RPBA Art. 12

Keyword:

Claim request - admitted (yes)

Sufficiency of disclosure - (yes)

Novelty - second (or further) medical use (yes)

Documents - admitted (no)

Inventive step - (yes)



Beschwerdekammern

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Case Number: T 0740/14 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 13 September 2018

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Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 24 January 2014
rejecting the opposition filed against European
patent No. 1778234 pursuant to Article 101(2)
EPC.**

Composition of the Board:

Chairman A. Lindner
Members: R. Hauss
M. Blasi

Summary of Facts and Submissions

I. European patent No. 1 778 234 was granted with a set of ten claims.

Independent claim 1 reads as follows:

"1. Pimobendan for use in the reduction of the heart size of a patient suffering from heart failure."

II. The patent was opposed under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

III. In the course of the opposition proceedings, the patent proprietor submitted several claim requests as auxiliary requests, including auxiliary request I filed with a letter dated 20 November 2013. The sole independent claim of that request reads as follows:

"1. Pimobendan for use in the reduction of the heart size of a patient suffering from heart failure, wherein the heart failure is accompanied with an increase of the heart size and deterioration of cardiac function."

IV. The documents cited in the opposition and appeal proceedings included the following:

D1: Intern J Appl Res Vet Med 5(1), 43-48 (2007)

D2: Freedom of Information Summary NADA 141-273,
Vetmedin Pimobendan Chewable Tablets Dogs (2007)

D4: Drugs and Aging 4(5), 417-441 (1994)

D5: Circulation 84, 796-804 (1991)

D8: Dictionnaire Médicaments Vétérinaires, 12th ed
2003, pages 1229-1230 (ISBN 2-86326-196-7)

- D9:** Boehringer Ingelheim: Ingelheimer Dialog June 2000, Luis-Fuentes, pages 8-11
- D10:** Angiology 29(6), 463-472 (1978)
- D11:** Veterinary Record 146, 687-690 (2000)
- D15:** J Cardiovasc Pharmacol 14 (Suppl. 2), S49-S56 (1989)
- D16:** J Am Anim Hosp Assoc 42, 249-261 (2006)
- D21:** Cardiology 88 (suppl 2), 28-36 (1997)
- D22:** J Pharmacol Exp Ther 282(1), 23-31 (1997)
- D23:** ICVS 04, 1st International Canine Valvular Disease Symposium, Paris, 30-31 October 2004, 1-84
- D24:** Rinsho Iyaku, 8(6), 1311-1351 (1992)
- D25:** Raw data and size distribution analysis of Comparative Example 2 of the patent in suit
- D26:** Boehringer Ingelheim: Chart "How to Calculate the Vertebral Heart Score" (no publication date)
- D27:** Full English translation of D24

V. The appeal by the opponent (appellant) is directed against the decision of the opposition division rejecting the opposition, announced on 16 December 2013 and posted on 24 January 2014.

As set out in the decision under appeal, documents D21 to D23, filed by the opponent three days before the date of the oral proceedings, were not admitted into the proceedings.

The opposition division considered that the suitability of pimobendan for attaining the claimed therapeutic effect (the reduction of heart size of a patient suffering from heart failure) was disclosed in the patent and the corresponding patent application and was supported by post-published documents D1, D2 and D16 (Article 100(b) EPC).

While pimobendan had been known for the treatment of certain types of heart failure, claim 1 related to the treatment of a new subgroup of patients who had heart failure and an enlarged heart. Since the cited prior-art documents, specifically D4 (in the light of D15), D8 and D9, did not disclose or discuss the reduction of heart size, they did not anticipate the subject-matter of claim 1 (Articles 100(a), 52(1) and 54 EPC).

According to document D5, which represented the closest prior art, milrinone was administered for reducing the enlargement of the heart after acute myocardial infarction. The objective technical problem was the provision of an alternative compound for the same therapeutic purpose. The use of pimobendan as defined in claim 1 would not have been obvious to the person skilled in the art since milrinone and pimobendan were structurally quite different, and the prior art did not provide any pointer which suggested replacing milrinone with pimobendan for use in the reduction of heart size. Hence, the subject-matter of the claims as granted involved an inventive step (Articles 100(a), 52(1) and 56 EPC).

- VI. In its statement setting out the grounds of appeal, the appellant requested the revocation of the patent and based its reasoning on, *inter alia*, documents D21, D22 and D23, asking that they be admitted into the proceedings.

- VII. The patent proprietor (respondent) requested the dismissal of the appeal and, with the reply to the statement setting out the grounds of appeal, submitted five sets of claims as auxiliary requests I to V.

The sole independent claim of auxiliary request I reads as follows:

"1. Pimobendan for use in the reduction of the heart size of a patient suffering from heart failure, wherein the heart failure is accompanied by an increase of the heart size and deterioration of cardiac functions."

VIII. Oral proceedings before the board were held on 13 September 2018.

With regard to the admission of evidence and requests, the appellant requested that documents D21 to D23 be admitted into the proceedings and that auxiliary requests I to V be held inadmissible. The respondent requested that documents D21 to D23 not be admitted.

In the course of the oral proceedings, the respondent withdrew its main request for dismissal of the appeal, thereby making auxiliary request I its highest-ranking claim request.

IX. The appellant's arguments may be summarised as follows:

Auxiliary request I - inadmissibility

The request was not identical to any of the requests presented in the proceedings before the opposition division and should have been filed at an earlier stage. Therefore, it should be held inadmissible pursuant to Article 12(4) RPBA.

Claim analysis

The definition of the patients according to claim 1 of auxiliary request I also covered patients who did not have a pathologically increased heart size. Therefore, the claim was not restricted to a therapeutic use. It should not be assessed as a purpose-related product

claim according to Article 54(5) EPC, but as a compound claim restricted solely by the suitability of the compound for the stated purpose.

Since claim 1 did not define a specific method of measurement, heart size could be measured by any suitable method.

Sufficiency of disclosure

Neither the data shown in table 1 nor those presented in figure 7 of the patent in suit and the application as filed would have rendered it credible at the filing date that pimobendan could be administered for reducing the heart size of patients suffering from heart failure. Nor had it been shown that such a size reduction had a therapeutic benefit which could be distinguished from the known treatment benefit of pimobendan in heart failure.

The supplementary data from post-published documents D1 and D2 were not helpful in this respect, since D1 taught that the alleged therapeutic effect was only transitory (thus, it was not achieved over the entire scope claimed) and D2 did not mention a significant reduction in heart size.

Document D25 (containing raw data) did not form part of the patent/application documents and therefore could not be used to supplement information not disclosed in table 1. This also applied to document D16, which reported further results relating to example 2.

Novelty

The subject-matter of claim 1 of auxiliary request I lacked novelty over the disclosure of documents D8, D9 (figures 1 and 2) and D4 (page 427, column 2, lines 24

to 31). D15 (page S53) and D24/D27 referenced in D4 were cited as supplementary documents. The reduction of heart size was not different from the known use of pimobendan in the treatment of heart failure, and claim 1 therefore related to the discovery of the effect underlying a known use of the compound.

Inadmissibility of evidence

The appellant had first submitted documents D21, D22 and D23 during the proceedings before the opposition division, in response to a submission by the respondent. These documents were *prima facie* relevant to the issue of novelty and should therefore be admitted into the appeal proceedings, even though it was conceded that document D21 did not disclose additional information. While D23 was an intermediate document published after the priority date of the patent in suit, it formed part of the state of the art because the priority of the patent was not valid.

Inventive step

Starting from the technical teaching of document D5, the technical problem to be solved was the provision of an alternative compound for use in the reduction of the heart size of a patient suffering from heart failure. In view of the skilled person's common general knowledge, the claimed subject-matter was obvious since pimobendan represented the arbitrary choice of a component falling into the same functional class of compounds (PDE III inhibitors) as milrinone, the compound used according to D5. Milrinone was also presented and claimed as an embodiment of the invention in the application as filed.

Starting from the technical teaching of document D5 that milrinone acted to reduce the heart size of

patients suffering from heart failure, the objective technical problem was the provision of an alternative compound for that same use. To that end, the person skilled in the art would have tried compounds belonging to the same class of pharmacologically active compounds as milrinone, namely PDE III inhibitors, the selection of pimobendan being an arbitrary choice from among those options.

In reaction to the adoption of an unexpected interpretation of claim 1 by the board, the appellant should be permitted to introduce a further approach which assessed inventive step starting from the technical teaching of document D27.

- X. The respondent's arguments may be summarised as follows:

Auxiliary request I - inadmissibility

With the exception of certain minor modifications, the claimed subject-matter corresponded to what had already been pursued in the proceedings before the opposition division with former auxiliary request I.

Claim analysis

Claim 1 related to a further medical use drafted in the format according to Article 54(5) EPC. The appellant's interpretation according to which the use defined in claim 1 was not restricted to a therapeutic indication (since it hypothetically involved the treatment of subjects not in need of therapeutic treatment addressing heart size) was unrealistic and resulted in an unfoundedly broad claim construction. Firstly, a person skilled in the art reading claim 1 would be aware that in the context of classification systems for heart disease, an "increase of the heart size" meant an

increase beyond the norm. Secondly, the person skilled in the art would be aware that the envisaged treatment, by reducing heart size, improved the pumping capacity of the heart, which was impaired in heart failure patients. In view of the resulting impact on cardiac output, this would readily be identified as a therapeutic benefit.

A person skilled in the art reading the patent in suit and its claims, or the claims of auxiliary request I, would also infer that the term "reduction of the heart size" in claim 1 meant specifically the relative change of the parameter "vertebral heart sum" (VHS) mentioned in the description, in particular in paragraph [0021]. In any case, unlike the VHS, the various parameters employed in the prior art cited against novelty (see documents D4, D15 and D24/D27) described findings relating to, or affected by, the heart's ability to contract. Owing to their "dynamic" nature, these parameters were unsuitable for ascertaining or monitoring cardiac enlargement.

Sufficiency of disclosure

The information provided in example 2 of the patent in suit and the application as filed was sufficient to render the claimed therapeutic application credible. The observed reduction in heart size was a technical effect which was different from the known benefit of pimobendan as a Ca^{2+} -sensitising agent.

Post-published document D1 confirmed the results of example 2. A six-month treatment providing a reduction in heart size (as disclosed in D1), even if that effect was not permanent, still represented a treatment success, considering that without treatment the patient's heart would have been further enlarged.

The data reported in D1 and D2 were comparable and roughly within the same range.

Novelty

Mitigating pathologic cardiac remodelling by reversely remodelling the size of the heart was a therapeutic target independent of, and different from, the known therapeutic use of pimobendan in the treatment of heart failure. This previously unknown therapeutic use of pimobendan was a functional technical feature which established novelty relative to the disclosure of documents D4, D8 and D9.

Inadmissibility of evidence

According to the appellant, documents D21, D22 and D23 were novelty-destroying since they allegedly disclosed the use of pimobendan for reducing heart size. However, in D21 and D22 there was no such disclosure. D23, published after the priority date of the opposed patent, did not form part of the state of the art. Irrespective of this, its content was not *prima facie* relevant. The documents had accordingly not been admitted into the proceedings by the opposition division, and the board should hold them inadmissible pursuant to Article 12(4) RPBA.

Inventive step

The problem to be solved according to the patent in suit was to provide a medication which allowed reversely remodelling the size of the heart to reduce the risk of death in patients with coronary diseases. This problem was solved by the provision of pimobendan for use in the reduction of heart size. While pimobendan had been in use in the treatment of heart failure, its effect on heart size had not been known

before the priority date of the opposed patent. Accordingly, the invention was based on a new therapeutic indication for pimobendan rather than on the identification of a specific patient group.

Document D5 did not disclose that milrinone was applied for reducing the size of the heart. The document merely mentioned the prevention of left ventricular remodelling. Since a different therapeutic indication was addressed and the pharmacologically active agent was also different, D5 was not really a suitable starting point for the assessment of inventive step. In any case, D5 did not point to pimobendan as a drug effective in reverse cardiac remodelling.

- XI. The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

- XII. The respondent requested that the decision under appeal be set aside and that the patent be maintained in amended form on the basis of one of the sets of claims filed as auxiliary requests I to V with the reply to the statement setting out the grounds of appeal.

Reasons for the Decision

1. Auxiliary request I - inadmissibility (Article 12 RPBA)
 - 1.1 The set of claims of auxiliary request I was filed by the respondent with the reply to the statement setting out the grounds of appeal, in conformity with Article 12(1) and (2) RPBA.
 - 1.2 According to Article 12(4) RPBA, while everything presented in conformity with Article 12(1) and (2) RPBA is, as a rule, to be taken into account, a board nevertheless has the power to hold inadmissible requests which could have been presented or were not admitted in the first-instance proceedings.
 - 1.3 Auxiliary request I does not meet either of these criteria for the following reasons:
 - 1.3.1 The claims of this request correspond largely to those of former auxiliary request I presented during the proceedings before the opposition division (see points III and VII above). In addition to minor modifications in the sole independent claim 1 ("accompanied with" was corrected to read "accompanied by" and "cardiac function" was replaced by "cardiac functions" in line with paragraph [0019] of the description), a claim dependency was corrected in claim 9, and a list in claim 10 indicating preferred mammalian patients was modified to read "primates including humans, dogs, cats and horses" instead of "a human, a canine species, a feline species and an equine species". The two claim requests are otherwise identical.

1.3.2 Since with the decision under appeal the opposition was rejected, the (non-)admittance of former auxiliary request I was not among the issues decided in the proceedings before the opposition division.

1.4 Hence, the board had no reason to hold auxiliary request I inadmissible pursuant to Article 12(4) RPBA.

2. Claim analysis

2.1 The appellant took the view that the term "increase" used in claim 1 of auxiliary request I did not necessarily imply a pathological state. Since claim 1 did not define to what extent heart size was increased, or cardiac function deteriorated, the definition of the patients according to claim 1 also covered subjects who did not have a pathologically enlarged heart.

2.2 The board comes to a different conclusion. In the circumstances of the present case, the claim can and should be interpreted in a technically sensible rather than an overly formalistic and literal manner. Based on common general knowledge in the field of cardiology (as summarised, for instance, in the patent in suit in paragraph [0007] corresponding to page 2, lines 9 to 18, of the application as filed), the person skilled in the art reading claim 1 would infer, since it is mentioned that heart failure is accompanied by an increase of heart size and deterioration of cardiac functions, that this relates to pathologically relevant cardiac remodelling which occurs, as a rule, in connection with heart failure.

2.3 As a consequence, the indication defined in claim 1 is a therapeutic indication and the claim is drafted appropriately in the format provided for in Article 54(5) EPC. Accordingly, the indication

"for use in the reduction of the heart size"

is to be regarded as a functional technical feature which has to be taken into account in the assessment of the claimed subject-matter with regard to sufficiency of disclosure and patentability.

- 2.4 Furthermore, it follows from this general context that reverse cardiac remodelling is intended. While claim 1 does not specify a particular method for measuring heart size, the method must be suitable for ascertaining a change in the actual heart size. It was uncontested that the parameter "VHS" employed in the patent in suit, expressed in the unit "v" meaning the length of a vertebra (see paragraphs [0021] and [0056] to [0058] and point 3.2 below), reflects heart size without being affected by variations in haemodynamic factors.
3. Sufficiency of disclosure (Article 83 EPC)
- 3.1 As set out above (see point 2.3), attaining the specified therapeutic effect is a functional technical feature of claim 1 of auxiliary request I. Thus, it has to be established whether the patent, or rather the application as filed, discloses the utility of pimobendan for the reduction of heart size.
- 3.2 Example 1 of the patent in suit does not relate to heart size and can be disregarded. In support of the plausibility of the therapeutic effect, the respondent relied on example 2 (see pages 13 to 16 of the application as filed corresponding to paragraphs [0052] to [0059] of the patent in suit), which describes a clinical study in the form of a double-blind randomised positive controlled multi-centre field trial carried

out on dogs with heart failure due to valve insufficiency.

The study was conceived to evaluate the clinical efficacy of pimobendan treatment at a daily dose of 0.4 to 0.6 mg/kg in comparison to an angiotensin-converting-enzyme (ACE) inhibitor treatment with benazepril hydrochloride at a daily dose of approximately 0.25 to 0.5 mg/kg body weight. Both treatments could be combined with furosemide (up to 8 mg/kg per day) or anti-arrhythmic drugs as appropriate. Dogs were examined on day 0 prior to first treatment and on days 7 and 56 after initiation of therapy. Among other parameters, the vertebral heart sum (VHS) was measured. This parameter, which is also called "vertebral heart scale", is determined on the basis of a lateral thoracic radiograph. In the lateral view, the shape of the heart closely corresponds to the shape of the cardiac septum, which is not involved in the contractile action of the heart. The longest axis and the short axis at the widest part of the cardiac silhouette are measured, added and expressed in terms of the number of vertebra lengths fitting into that distance (see paragraph [0058] of the patent in suit and document D26).

It is reported in example 2 (see page 15, line 29, to page 16, line 8, of the application as filed) that the mean VHS measured on radiographs of days 0 and 56 showed improvement for dogs in the pimobendan group, indicating a reduction (by -0.15 v) in mean heart size for pimobendan-treated dogs, while the mean scores in the benazepril comparative group showed deterioration (by +0.22 v).

3.3 The appellant argued that the data reported in example 2 could not be regarded as conclusive, for the following reasons:

- (a) The data as presented in table 1 and figure 7 were inconsistent and not statistically significant.
- (b) The data were not reliable due to inter-operator variability.
- (c) The concomitant administration of furosemide might have affected the results observed.

3.4 These objections are not convincing, for the following reasons:

- (a) While - as pointed out by the appellant - the meaning of the values presented in the third row of table 1 of example 2 is not readily apparent, this is immaterial. The findings relevant to the reduction in heart size are reported in the text immediately preceding table 1, where it is mentioned that the mean vertebral heart sum measured on radiographs on days 0 and 56 showed improvement for dogs in the pimobendan group. With regard to the changes from baseline, the difference in the mean value indicated a reduction in mean heart size for pimobendan treated dogs, while the mean scores in the control benazepril group showed deterioration. It is also mentioned in that context that the difference between the treatment groups was statistically significant in favour of pimobendan treatment ($p < 0.0001$).

In addition, quantitative values are reported, namely the difference observed between standard therapy with a deterioration of mean heart size by 0.22 v and pimobendan treatment with an improvement of mean size of -0.15 v compared to baseline (see point 3.2 above and page 15, line 29,

to page 16, line 8, of the application as filed). There is no need to consider figure 7, which does not add any information but merely represents a graphic summary of these data.

The appellant questioned the validity of the results of the clinical study on the basis of the values indicated in table 1 for the median and standard deviation. However, these values taken by themselves cannot support a conclusive reasoning against the validity of the data reported in example 2. The fact that there was no difference between the median at visit 1 and visit 3 in the pimobendan group does not allow any definite conclusion to be drawn regarding a trend in the data. Also, considering the standard deviation in isolation is inappropriate, since it cannot be inferred from the standard deviation alone that there is no relevant difference between the mean values. Thus the appellant's conclusions on the validity of the data are neither straightforward nor inevitable.

- (b) According to document D11 invoked by the appellant (see page 688, column 2, "Results", paragraph 4 and page 690, column 1, lines 18 to 20), the inter-operator variability in determining the VHS may be as high as 10%. The observers contributing to the data presented in D11 (an experienced veterinary radiologist, a medicine resident and a veterinary nurse) were not, however, equally trained and therefore did not have comparable skills. In fact, the observers were intentionally chosen to provide a range of radiographic abilities (see D11: page 688, column 1, lines 1 to 5). While this may mean that appropriate training is required for reliably determining the VHS, the

statements in document D11 are not suitable for challenging the validity of the data presented in the patent in suit since - even though the study in question was a multi-centre study - there is no evidence of high inter-operator variability occurring in the present case (and, in particular, between visits 1 and 3 at the same centre). Thus, the appellant's objection in this regard remains speculative.

- (c) While the treatment of the dogs in example 2 could include the concomitant administration of furosemide (see point 3.2 above), this was the case for both treatment groups and there is no specific reason to believe that furosemide had an effect on heart size (whether by itself or by interaction with the co-administered drugs).

In this context, the appellant referred to document D10, which is a scientific article on the acute effects of furosemide on blood electrolytes, haemodynamics and urinary output in dogs. However, the content of D10 is not relevant, since it relates to the monitoring of various haemodynamic parameters following a single administration of furosemide (see D10: page 465, lines 31 to 37; page 471, last paragraph) and does not refer to heart size at all. The reduction of blood volume due to the diuretic effect of furosemide is not correlated to heart size.

- 3.5 Thus, the data reported in example 2 are sufficient to establish at least the initial plausibility of the therapeutic application of reducing heart size.

3.6 In accordance with the established case law of the boards of appeal, additional evidence may therefore be taken into account.

3.6.1 Document D25 presents raw data of the study reported in example 2 of the patent which corroborate the information provided in the patent and the application as filed.

3.6.2 Post-published document D16 relates to the same study and reports that in an analysis of the subgroup of dogs treated concomitantly with furosemide, it was found that the mean VHS decreased in the pimobendan-treated group and increased in the benazepril-treated group, and that the difference was statistically significant (see D16: page 257, left column). This supports the respondent's argument that a statistically significant difference between the treatment with pimobendan and benazepril can also be observed under the concomitant administration of furosemide.

3.7 The appellant cited post-published document D1 in support of its argument that the therapeutic benefit "reduction of the heart size" was not achieved over the entire scope claimed.

According to D1 (abstract), the effect of pimobendan and the ACE inhibitor ramipril on the vertebral heart size in dogs with congestive heart failure was investigated. The administration of pimobendan resulted in a reduction in VHS at months 1 and 3 of treatment with an increase at month 6, while in the ramipril group, an increase in VHS occurred at months 1, 3 and 6. As shown in figure 1 of D1, the treatment with pimobendan led to an absolute decrease in VHS, whereas with ramipril, a progressive further increase of the heart size was observed.

The results observed with pimobendan are in line with example 2 of the patent in suit. Even if the reduction in heart size was temporary (several months), this represents a therapeutic success. There is no requirement in claim 1 that a permanent reduction in heart size must be achieved and no indication that such an embodiment is targeted by the claim. Hence, the appellant's objection must fail.

3.8 In post-published document D2, the results observed with the treatment of dogs suffering from heart failure with pimobendan (the active agent of "Vetmedin" tablets administered according to D2) in comparison to treatment with the ACE inhibitor enalapril maleate are presented.

Based on table 6 on page 11 of D2, the appellant argued that the reduction in heart size achieved with pimobendan was weak and that "normal" VHS values, i.e. values within the range found in healthy subjects, were not achieved.

However, since claim 1 does not require a return to the "healthy" range and a complete reversal is not possible, this is not relevant. Since it is common general knowledge that an enlarged heart has a deteriorated cardiac output, causing a number of unfavourable symptoms, the person skilled in the art would see a therapeutic benefit in reducing heart size.

3.9 Both D1 and D2 illustrate a reduction of heart size achieved upon treatment with pimobendan - in line with the disclosure of the patent in suit. In both cases, the comparative drug did not achieve a reduction in heart size. Thus, the post-published results of documents D1 and D2 confirm the observations reported in the patent in suit.

- 3.10 As a consequence, the subject-matter claimed in auxiliary request I is disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.
4. Novelty (Articles 52(1), 54(1), (2) and (5) EPC)
- 4.1 As already mentioned (see point 2.3 above), the indication defined in claim 1 of auxiliary request I "for use in the reduction of the heart size" is to be taken into account as a functional technical feature in the assessment of novelty and inventive step.
- 4.2 The appellant contended that the treatment was inherent to the known treatment of administering pimobendan against heart failure and that the indication "reduction of the heart size" merely provided an explanation for the known efficacy of pimobendan.
- 4.3 The board arrives at a different conclusion. An inotrope is an agent that alters the force of the contractions of the heart muscle. Pimobendan was previously known as a positive inotropic agent increasing the contractility of the heart, thereby providing a symptomatic relief in patients suffering from heart failure. The reduction of heart size is not an explanation ("underlying effect") for this known therapeutic use of pimobendan, since the mechanisms of action and the resulting therapeutic effects are different. It is thus evident that reverse remodelling is an independent therapeutic use. While the reduction of heart size may be inherent to the treatment with pimobendan, if this specific use was not disclosed in the prior art, it confers novelty on the claimed subject-matter.

4.4 Document D8

4.4.1 Document D8 is an excerpt from a dictionary relating to veterinary medicines and discloses the properties and therapeutic uses of Vetmedin[®], a medicament containing pimobendan for dogs. According to D8, the therapeutic indication of Vetmedin[®] is congestive heart failure due to dilated cardiomyopathy. D8 mentions the activity of pimobendan as a Ca²⁺ sensitising agent and PDE III inhibitor, which results in a vasodilatory and positive inotropic effect.

4.4.2 This activity and use are different from the reduction of heart size defined in claim 1 of auxiliary request I, even if the patients to be treated with Vetmedin[®] may have an enlarged heart. The efficacy of pimobendan for reducing heart size cannot be derived from the information presented in document D8, which therefore does not anticipate the subject-matter of claim 1.

4.5 Document D9

4.5.1 Document D9 relates to an animal study presumed to be identical to the study described in example 1 of the patent in suit and does not mention any effect of pimobendan on heart size, which was not a parameter of interest. Rather, the aim of the study of D9 was to evaluate the long-term efficacy and tolerance of pimobendan as a positive inotropic agent in cocker spaniels and dobermans with dilated cardiomyopathy and its effect on survival.

4.5.2 It is explained in document D9 that figure 1 shows the lateral thoracic radiograph of an English cocker spaniel with dilated cardiomyopathy (the comment underneath figure 1 states that there is evident hypertrophy), and figure 2 shows the lateral thoracic

radiograph of the same animal after four months' therapy with furosemide, enalapril, digoxin and pimobendan. The appellant contended that even without the indication of VHS values, an experienced observer (i.e. a person skilled in the art) would, by subjective assessment, readily deduce from figure 2 of D9 that a reduction of the heart size was achieved. However, a comparison of the two figures without further information cannot lead to conclusive results since several drugs were employed, a comparative figure obtained with placebo treatment is missing and, moreover, it also appears that the resolution of the two pictures is different. Thus, it cannot be inferred conclusively from a comparison of figures 1 and 2 that the administration of pimobendan is effective for reducing heart size.

4.6 Document D4

4.6.1 Document D4 is a review article on pimobendan which mentions the known inotropic and peripheral vasodilator properties of the drug but does not discuss the use of pimobendan in the reduction of heart size.

4.6.2 As a review article, D4 only summarises the results of other papers. In support of its objection regarding lack of novelty, the appellant relied on the following passage on page 427, column 2, lines 24 ff of D4:

"Significant reductions in the radiologically determined absolute heart volume (8%) and cardiothoracic ratio (3%), as well as the echocardiographically determined left ventricular end-systolic diameter (3%), were obtained after 2 to 8 weeks' oral treatment with pimobendan 2.5 or 5 mg twice daily in patients with chronic heart failure (Hauf et al. 1989; Kato et al. 1992)."

The cited publications are D15 (Hauf, see page S53, column 2) and D24 (Kato, translation: see D27).

4.6.3 The study described in document D15 involved a two-week treatment phase to examine the haemodynamic efficacy of pimobendan in comparison with the ACE inhibitor captopril in human subjects (see the title of D15 and page S49, column 2, fifth line from the bottom). Thus, D15 is not primarily concerned with the size of the heart. The VHS was not determined.

(i) D15 reports that both treatment groups were treated with digitalis and diuretics and, after randomisation, either pimobendan or captopril as additional medication. A reduction in the radiologically determined absolute heart volume could be observed in both treatment groups after a two-week therapy, while the decrease in heart volume relative to body weight was insignificant.

Irrespective of how the heart volume was determined and whether/how the result obtained correlates with heart size (see point 4.6.4(ii) below), since both treatments resulted in a reduction of heart volume and other medicaments were concomitantly administered, it is not directly and unambiguously disclosed in D15 that the administration of pimobendan resulted in a reduction of heart volume, or heart size.

(ii) D15 further reports that the left-ventricular end-systolic diameter showed a slight but significant decrease under pimobendan.

It was not shown that this result is meaningful for the present purpose of establishing that the claimed subject-matter is anticipated by the prior art. In fact, this appears doubtful, since D15 also reports that the left-ventricular end-diastolic diameter did not change significantly. As explained by the respondent, the therapeutic effect of

positive inotropic agents such as pimobendan is improved contractility of the heart, which may result in, *inter alia*, a reduced end-systolic volume due to increased muscular action.

For these reasons, no definite conclusion can be drawn on the basis of the information provided in document D15 about the effect of pimobendan on heart size.

4.6.4 Document D24 relates to a clinical study which was carried out with human patients to assess the safety and efficacy of pimobendan in chronic heart failure, in comparison with placebo. D24 reports that the parameters "cardiothoracic ratio" and "left-ventricular end-systolic dimension" were significantly decreased in the pimobendan group but not in the placebo group, after four and eight weeks of treatment (see D27: page 15, lines 19 to 31, and page 7, lines 24 to 39). The VHS was not determined.

(i) As far as the results reported for the left-ventricular end-systolic dimension (or diameter) are concerned, the remarks in point 4.6.3(ii) above apply in the same way. Again, the left-ventricular end-diastolic dimension did not change significantly (see D27: page 15, lines 27 to 29, LVDd).

(ii) The appellant argued, with reference to document D11, that the cardiothoracic ratio, like the VHS, was indeed a parameter describing the size of the heart (see D11: page 689), and according to D24 its value had decreased upon treatment with pimobendan.

In this context, the respondent pointed out that the VHS, which was determined on the basis of a

lateral thoracic radiograph, and thus a side view of the heart, was a suitable measure for static heart size (see points 2.4 and 3.2 above), while the cardiothoracic ratio was not. The determination of the cardiothoracic ratio was based on a front or back view radiograph of the thorax and was calculated by dividing the cardiac diameter by the thoracic diameter. The determination of the cardiothoracic ratio involved some uncertainty due to the variable contractile status of the heart when the X-ray radiograph was taken. If the cardiothoracic ratio was determined as a mean value obtained from several measurements, it must necessarily reflect the effect of a drug which enhanced the contractility of the heart, i.e. a haemodynamic parameter. Thus, the decrease in the cardiothoracic ratio reported in document D24 did not necessarily indicate that the actual size of the heart was decreased. It might merely reflect an increase in the contractility of the heart muscle. The same objection applied in principle to the radiologically determined heart volume mentioned in document D15 (see point 4.6.3(i) above).

Document D24 merely reports changes in the cardiothoracic ratio but does not draw any explicit conclusion with regard to a change in heart size. Taking the respondent's arguments into account, it cannot be directly and unambiguously inferred from the information presented in D24 that pimobendan has the effect of reducing heart size.

4.7 For these reasons, the subject-matter of claim 1 and the dependent claims of auxiliary request I is novel relative to the disclosure of documents D4, D8 and D9.

5. Inadmissibility of evidence (Article 12(4) RPBA)

5.1 Documents D21 to D23 were cited by the appellant in its statement setting out the grounds of appeal. As set out in the decision under appeal (see point V above), D21 to D23 had previously not been admitted into the proceedings by the opposition division. It was thus within the board's discretionary power pursuant to Article 114(2) EPC and Article 12(4), first half-sentence, RPBA to hold these documents inadmissible.

5.2 Documents D21, D22 and D23 were first cited by the appellant in a letter dated 13 December 2013, i.e. one working day before the oral proceedings scheduled by the opposition division. They were thus presented after the final date according to Rule 116(1) EPC for making written submissions in preparation for the oral proceedings before the opposition division.

The appellant submitted that these documents disclosed the use of pimobendan in the reduction of heart size. Thus, they were cited against novelty. In the case of intermediate document D23, this objection was combined with the new objection that the priority of the patent was not validly claimed.

In its letter of 13 December 2013, the appellant stated that documents D21 to D23 were filed in direct response to the respondent's new auxiliary requests presented with the letter dated 20 November 2013, in which the feature "for use in the treatment" was replaced by the feature "for use in the reduction of the heart size". Later, the appellant also stated that D21 to D23 had been filed in support of certain statements in document D4 which had been questioned only recently.

However, this cannot justify the appellant's timing since the feature "for use in the reduction of the heart size", known to be crucial to the case, was already present in the claims as granted (corresponding to the respondent's then pending main request). Nor did the appellant show a complementary relationship between document D4 and documents D21, D22 or D23.

Hence, documents D21, D22 and D23 were indeed not presented in due time in the proceedings before the opposition division, and the opposition division had the power of discretion pursuant to Article 114(2) EPC concerning their admission.

5.3 The opposition division heard the parties on the admission of documents D21 to D23 (see the minutes of the oral proceedings before the opposition division, point 2). In its considerations (see the decision under appeal, point II.3.2), the opposition division applied the criterion of *prima facie* relevance, also mentioning that the objection relating to the validity of the priority claim had been raised for the first time (criterion of procedural economy).

Thus, the opposition division used the correct criteria in the exercise of its discretion. The board had no reason to assume that the opposition division applied its discretion in an unreasonable way.

5.4 Moreover, the board arrived at the same conclusions as the opposition division regarding the relevance of documents D21 to D23 (see points 5.5 to 5.7 below).

5.5 Document D21

5.5.1 D21 is a review article summarising the results of previous Japanese studies on the clinical efficacy and safety of pimobendan (see page 28, bottom of column 2).

5.5.2 For its objection regarding lack of novelty, the appellant relied on a passage of D21 summarising the results presented in document D24 (see pages 32 and 33 and reference [32] of D21). As conceded by the appellant, document D21 does not however provide additional information going beyond the content of the documents already on file (see D24, and D4 as far as it relates to D24). Thus, document D21 is not of higher relevance than the documents already on file.

5.6 Document D22

5.6.1 Document D22 investigates the effect of pimobendan on the left ventricular systolic and diastolic performance at rest before and after pacing-induced congestive heart failure in dogs.

5.6.2 The document does not contain any passage referring unambiguously to a reduction of heart size (also see the decision under appeal, II.3.2).

No correlation between the parameters of D22 invoked by the appellant and heart size is apparent. Based on the comparison of the left ventricular end-diastolic and left ventricular end-systolic volume shown in Tables 1 and 3 of D22, the appellant concluded that the administration of pimobendan resulted in a reduction of heart size. Actually, the aim of D22 was the evaluation of the known positive inotropic effect and the arterial vasodilatory action of pimobendan in comparison to amrinone. As explicitly mentioned, the therapeutic effect observed in D22 is enhanced contractility (see D22: abstract, last sentence). The appellant's submissions in the appeal proceedings did not introduce any new aspect concerning the assessment of D22.

5.7 Document D23

5.7.1 The appellant contended that the priority of the patent in suit was not validly claimed, that, therefore, document D23 (published after the priority date and before the filing date of the patent) was part of the state of the art pursuant to Article 54(2) EPC and that the claimed subject-matter lacked novelty vis-à-vis the disclosure of document D23 (page 70).

5.7.2 It was not contested by the appellant that the wording of the claims of auxiliary request I had a correspondence in passages of the priority application (European patent application No. 04 007 179.7). The appellant based its reasoning disputing the validity of the priority claim on the absence of figure 7 and of data relating to benazepril from example 2 as reported in the priority application (see page 15, lines 4 to 15 of the priority application in comparison with page 16, lines 6 to 8 and figure 7 of the application as filed). The appellant argued that, since that information was missing, the disclosure of the priority application was not enabling for the therapeutic indication "for use in the reduction of the heart size".

5.7.3 The board reached a different conclusion. The priority document describes the setup of the clinical study conducted according to example 2 and reports the following results:

"The mean vertebral heart sum measured on radiographs on days 0 and 56 showed improvement for dogs in the pimobendan group, while the mean scores in the control benazepril group showed deterioration. With regards to the changes from baseline, the difference in the mean value indicated a reduction in mean heart size for pimobendan treated dogs. The mean difference between the groups regarding overall clinical efficacy was

statistically significant in favour of pimobendan treatment ($p < 0.0001$)."

The board considered that this information, although the improvement or deterioration is not quantified, was sufficient to establish the plausibility of the therapeutic indication and is therefore enabling.

5.7.4 Since the priority of the patent in suit is valid, document D23 is not part of the state of the art according to Article 54(2) EPC.

5.8 For these reasons, the board exercised its power of discretion pursuant to Article 12(4) RPBA to hold documents D21 to D23 inadmissible.

6. Inventive step (Article 52(1) and 56 EPC)

Patent in suit

6.1 The patent in suit (see paragraph [0007]) explains that it is known that the progress of heart failure is associated with an increase in heart size. Dilated cardiomyopathy usually involves cardiac remodelling that may be defined as genome expression and molecular, cellular, and interstitial changes manifested clinically as changes in size, shape, and function of the heart. Cardiac remodelling is generally an adverse sign and linked to heart failure progression. Reverse cardiac remodelling is a goal of the treatment of heart failure therapy. The patent seeks to provide a medication which allows remodelling heart size to reduce the risk of death in patients with coronary diseases (see paragraph [0009]).

6.2 The solution to this problem claimed in auxiliary request I involves pimobendan for reverse cardiac remodelling.

Starting point in the prior art

- 6.3 Document D5 was used by the appellant and by the opposition division as the starting point for the assessment of inventive step.
- 6.4 D5 reports that milrinone, which is a PDE inhibitor with positive inotropic and vasodilator properties, attenuates progressive left-ventricular dilation occurring after acute myocardial infarction in rats.

Technical problem and solution

- 6.5 The subject-matter of claim 1 of auxiliary request I differs from the disclosure of document D5 at least in the pharmacologically active agent to be used, which is pimobendan instead of milrinone.
- 6.6 The respondent contended that, furthermore, the reduction of heart size after cardiac remodelling had already occurred, as addressed in claim 1, was different from merely attenuating the progression of left-ventricular remodelling addressed in document D5.
- 6.7 As set out in section 3 above, it was rendered credible that pimobendan has therapeutic benefit in reducing heart size.
- 6.8 Assuming in the appellant's favour that the therapeutic purpose addressed in D5 is the same as in the patent in suit, the objective technical problem to be solved is the provision of an alternative compound for the therapeutic purpose of reverse cardiac remodelling.
- 6.9 The technical problem is solved by the subject-matter defined in claim 1.

Obviousness of the solution

6.10 Document D5 is exclusively concerned with milrinone and does not teach that further compounds may be effective in reducing heart size. Pimobendan is not mentioned.

6.11 While milrinone, like pimobendan, was known as a PDE III inhibitor with positive inotropic and vasodilator properties, the two compounds are structurally quite different (milrinone = 1,6-Dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile; pimobendan = 4,5-Dihydro-6-[2-(4-methoxyphenyl)-1H-benzimidazol-6-yl]-5-methyl-3(2H)-pyridazinone). Neither common general knowledge nor any teaching in D5 or any other document of the prior art on file would have suggested to the person skilled in the art that all PDE III inhibitors, or more specifically, pimobendan, would act to reduce the size of the heart.

6.12 The activity of pimobendan in reducing heart size is therefore surprising. As a consequence, the subject-matter of claim 1 and the dependent claims involves an inventive step within the meaning of Article 56 EPC.

7. Admission of a new line of argument

7.1 During the oral proceedings before the board of appeal, the appellant stated that it intended to base its reasoning on inventive step also on a second approach starting from the technical teaching of document D24. The appellant contended that this line of argument should be admitted since it was raised in response to the board acknowledging the novelty of the claimed subject-matter vis-à-vis the disclosure of D4 (in view of the secondary document D24) as a consequence of a surprising interpretation of the term "heart size".

- 7.2 The inventive-step assessment starting from the teaching of document D24 was first mentioned by the appellant on the day of the oral proceedings before the board of appeal and constitutes a change of the appellant's case. Its admission is thus subject to the board's power of discretion pursuant to Article 13(1) RPBA.
- 7.3 In its assessment of the novelty of the claimed subject-matter relative to the disclosure of document D4 (in view of D24), the board basically agreed with the view held by the respondent and the opposition division in this regard. Hence, the appellant's submission was not occasioned by a new development in the form of new points raised in the proceedings.
- 7.4 For this reason, the board did not admit the appellant's new line of argument into the proceedings (Article 13(1) RPBA).

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 in amended form on the basis of the set of claims filed as auxiliary request I with the reply to the statement setting out the grounds of appeal, and a description and drawings adapted thereto.

The Registrar:

The Chairman:



M. Schalow

A. Lindner

Decision electronically authenticated