

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2018/080226

International filing date (day/month/year)
06.11.2018

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07.11.2017

International Patent Classification (IPC) or both national classification and IPC
INV. C07D261/04 A61K9/00 A61K9/14 A61P33/14 A61K31/42 A01N43/80

Applicant
INTERVET INTERNATIONAL B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:



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Date of completion of
this opinion

see form
PCT/ISA/210

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-24</u>
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>1-24</u>
Industrial applicability (IA)	Yes: Claims	<u>1-24</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- | | |
|----|--|
| D1 | US 2016/256442 A1 |
| D2 | WO 2011/149749 A1 |
| D3 | WO 2010/149727 A2 |
| D4 | WO 2017/108954 A1 |
| D5 | XP021179157 (Kilp, S. et al., Parasites & Vectors, vol. 7, no. 1 (2014), p. 85-89) |

The application relates to an injectable pharmaceutical composition comprising particles of an isoxazoline compound of the general Formula (I) (preferred compound: fluralaner) and a pharmaceutically acceptable excipient. The particles are characterized in that they have a volume weighted particle distribution D50 of from 25 to 250 microns as measured by a static light scattering instrument. A method of treating or preventing a parasite infestation in an animal by administering the injectable pharmaceutical composition and a kit are also claimed.

Novelty

D1, D2 and D5 disclose isoxaline compounds which fall within the general Formula (I) as defined in present claim 1 and their suitability for the treatment of parasite infestation in animals by injection (cf. D1, abstract and Examples 22-23; D2, abstract, claims and pages 48-49; and D5, abstract).

However, the particle size distribution of the particles in the injectable pharmaceutical composition is not disclosed in D1, D2 or D5.

D3 and D4 do not relate to isoxaline derivatives.

The presently claimed subject-matter is thus novel over the available prior art (Article 33(2) PCT).

Inventive Step

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 1-24 does not involve an inventive step.

D1 and D2 also disclose isoxazoline compounds for the treatment of parasite infestation in animals by injection. The presently claimed injectable pharmaceutical compositions differ from these prior art documents in that the isoxazoline particles in said composition are specified as having a volume weighted particle distribution D50 of from 25 to 250 microns as measured by a static light scattering instrument.

On page 2, lines 20-22 of the present application, the problem to be solved is described as the provision of injectable isoxazoline compositions with long term efficacy against parasites and reduced risk of injection site irritation.

The use of isoxazoline particles having a volume weighted particle distribution D50 of from 25 to 250 microns as measured by a static light scattering instrument for the injectable pharmaceutical composition is suggested as a solution to this problem.

However, said solution is not considered inventive for the following reasons:

The effect of the particle size and particle size distribution of suspended pharmaceutically active compounds in compositions for injection is well-known in the prior art, see for example D3, page 3, paragraph [0008]. It is clear from said paragraph that a larger particle size needs to be chosen if a long-lasting effect after injection is desired. It is also clear from paragraph [00080] on pages 25-26 of D3 that particle fractions with small D50 values or having a large "fines" content tend to exhibit a "bursting effect" or "Burst Release" upon injection and are thus unacceptable for use as a formulation for depot administration.

Moreover, Example 2 and Table 4 on pages 39 and 40 of the present application are said to demonstrate that injection site irritation of the compositions with smaller fluralaner particle size was more severe than those with a larger particle size (cf. page 41, first paragraph).

However, it appears that the data in Table 4 are not suitable to demonstrate a direct link between the volume weighted particle size and the injection site irritation in the dogs. For Example 1B with a volume weighted particle size of 10µm, for example, very little irritation is observed, while for Example 1D with a volume weighted particle size of 40µm, the information "4 dogs unresolved" appears to imply that there is still some irritation even 20-21 days after injection.

In the absence of more conclusive data, the problem of providing an injectable pharmaceutical composition having a reduced risk of injection site irritation cannot be considered to be solved.

It is additionally mentioned that since the skilled person would in any case choose particles having a larger average size in order to provide a long-lasting effect and avoid a "bursting effect" as described in D3, a possible problem in connection with the injection site irritation would automatically be solved, i.e. said potential additional effect in connection with the particle size distribution would be considered a mere bonus effect.

The amounts of the isoxazoline compound in the composition as specified in present claims 6-8 as well as the use of a further parasiticide compound such as the macrocyclic lactone derivatives milbemycin and moxidectin as specified in present claims 10-13 are known for example from D1 (see D1, claims 22-26) and can therefore not impart an inventive step either.

Industrial Applicability

Industrial applicability is acknowledged.

Re Item VII

Certain defects in the international application

According to Rule 6.4(c) PCT, all dependent claims should be grouped together to the extent and in the most practical way possible. Claim 21 which is a dependent claim directed to an injectable pharmaceutical composition should thus be grouped together with claims 1-14.

Re Item VIII

Certain observations on the international application

- 1 Claims 15-20 and 24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT.

For the assessment of the present claims 15-20 and 24 on the question whether they are patentable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as patentable the subject-matter of claims to the use of a compound in medical treatment, but may allow claims to compounds or compositions for use in a first or further medical treatment.
- 2 Claim 1 is directed to an injectable pharmaceutical composition comprising particles of a compound of Formula I characterized by a certain volume weighted particle size distribution.

Claim 2 further specifies that the isoxazoline compound is in suspension in the composition. Since a dependent claim normally further delimits the scope of the claim(s) to which it refers, claim 2 renders the scope of claim 1 unclear since it appears to imply that claim 1 could be a composition other than a suspension (Article 6 PCT). In particular, it raises doubts as to whether the wording "injectable pharmaceutical composition" in claim 1 defines a liquid composition which could be directly injected, or might also encompass a solid crystalline mixture yet to be mixed with a liquid vehicle as specified in claim 22. Claim 1 should thus be defined as a suspension as disclosed in claim 2.
- 3 The expression "about" in claims 1, 3, 4, 6, 7, 8, 14, 21 and 22 is vague and indefinite and renders the scope of the claims unclear (Article 6 PCT).
- 4 Claim 1 (definition of the variable n) contains further preferred features which define a second scope of protection within one claim. This renders the scope of the claim unclear (Article 6 PCT).

It could also be argued that these features are simply non-limiting for the claim. In this case, they are superfluous, and the requirement of conciseness is not met (Article 6 PCT).

Such further preferred features have to be deleted or formulated in a separate dependent claim.

- 5 The wording "wherein the composition is to be reconstituted with a vehicle" in claim 9 leaves the reader in doubt as to which technical features could be implied that could further delimit the composition claims to which claim 9 refers. Claim 9 therefore does not meet the requirement of clarity and conciseness (Article 6 PCT).
- 6 Claim 16 merely contains a statement of a result to be achieved ("wherein the animal suffers minimal injection site irritation"), without specifying the technical features necessary to achieve said result which could further delimit the subject-matter of claim 15 to which claim 16 refers. Claim 16 therefore does not meet the requirements of Articles 5 and 6 PCT.
- 7 It is not clear from the wording of claim 22 whether the solid crystalline isoxazoline compound and the vehicle for forming a suspension with said crystalline compound are in the same or separate containers. This renders the scope of claims 22 and 23 unclear (Article 6 PCT).
- 8 Claim 24 is directed to a method of treating or preventing a parasite infestation in an animal which comprises the administration of the kit as defined in claims 22 and 23. However, it is not evident how a kit containing at least two containers and instructions could be administered to an animal (Article 5 and 6 PCT).
- 9 The unit "microns" employed in claims 1, 3, 4, 21 and 22 is not additionally expressed in terms of the units stipulated by Rule 10.1(a) PCT.

- 10 According to page 12, lines 1-2, the isoxazoline compounds for use in the invention also include esters thereof. Since this is not apparent from the wording of the claims, said passage in the description renders the scope of the claims unclear (Article 6 PCT).
- 11 It appears that only the Examples 1D, 1I and 1J in Table 3 on pages 35-37 are according to the invention as claimed. The remaining examples should therefore be identified as not according to the invention (Article 6 PCT).
- Moreover, it is noted that the particle size indicated for Example 1I in Table 4 on page 40 does not correspond to the particle size indicated for the same example in Table 3 on page 37. Clarification is kindly requested (Article 6 PCT).
- 12 The sentence on page 28, lines 8-10 appears incomplete and should be checked.