| IN THE UNITED STATES PATENT AND TRADEMARK OFFICE | |
|---|---|
| In re the application of: | Confirmation No.: 4760 |
| Hubert Rast *et al.* | Group Art Unit: 1625 |
| Patent Serial No.: 7,977,484 | Examiner: N/A |
| Filed: November 5, 2007 | Attorney Docket No.: BHC 031064<br>2920951-000297 |
| For: | NOVEL CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL) -6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID |

* * * * * *

**APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C § 156**

Filed via EFS
U.S. Patent and Trademark Office

Sir:

ELANCO ANIMAL HEALTH GMBH, formerly known as BAYER ANIMAL HEALTH GMBH, is the assignee of U.S. Patent No. 7,977,484 (the "'484 Patent"), as evidenced by the first assignment recorded on December 11, 2007 at Reel/Frame 020224/0985, the second assignment recorded on February 5, 2009 at Reel/Frame 022213/0726, the third assignment recorded on April 1, 2013 at Reel/Frame 030127/0549, the fourth assignment recorded on February 8, 2024 at Reel/Frame 066525/0898, and the fifth assignment recorded on February 7, 2024 at Reel/Frame 066401/0955, copies of which are attached hereto as Exhibit A. ELANCO ANIMAL HEALTH GMBH (the "Applicant") hereby submits this application for extension of patent term for the '484 Patent under 35 U.S.C § 156, by providing the following information as required by 37 C.F.R. § 1.740.[1]

[1] ELANCO ANIMAL HEALTH GMBH, the patent owner, and ELANCO US, INC, the applicant for regulatory approval of Pradalex®, are wholly owned subsidiaries under the common control of the same parent company Elanco Animal Health Inc.. (Exhibit J). As such, Elanco Animal Health GMBH has the right to reference the regulatory files necessary to file this application.

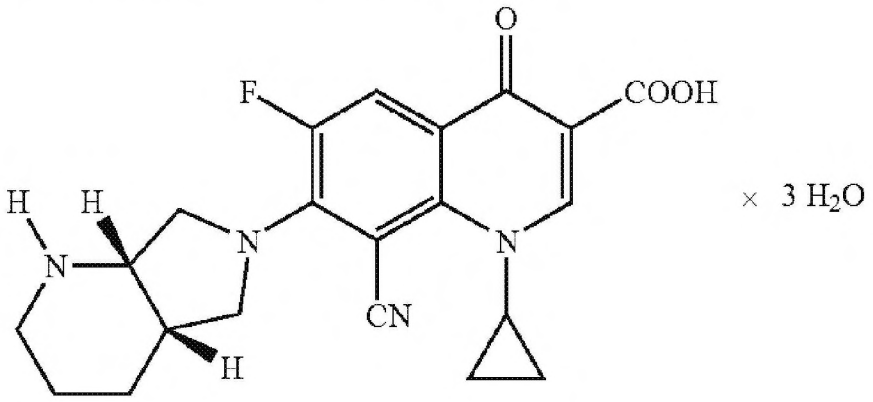
**1. A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics.**

The approved product is PRADALEX®, a product that contains pradofloxacin, in the form of pradofloxacin trihydrate for use in the treatment of bovine respiratory disease, and swine respiratory disease. A copy of the product label of PRADALEX® is attached hereto as Exhibit B.

Pradofloxacin trihydrate, a fluoroquinolone carboxylic acid, is a member of the class of 8-cyano-fluoroquinolone compounds. The chemical name of pradofloxacin trihydrate is 8-cyano-1-cyclopropyl-7-(1S,6S)-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline carboxylic acid trihydrate.

The primary mode of action of pradofloxacin trihydrate involves interaction with the enzymes essential for the major DNA functions of bacteria like DNA replication, transcription and recombination. The primary targets for pradofloxacin trihydrate are the bacterial DNA gyrase and topoisomerase IV enzymes where reversible association between them and pradofloxacin results in inhibition of these enzymes and death of the bacterial cell.

The structural formula of pradofloxacin trihydrate is:




**2. A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred.**

Regulatory review of pradofloxacin trihydrate occurred under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b).

**3. An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred.**

The pradofloxacin trihydrate product received permission on April 9, 2024 for commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b). A copy of the approval letter is attached hereto as Exhibit C.

**4. In the case of a drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.**

The approved product, PRADALEX®, includes the active ingredient pradofloxacin, in the form of pradofloxacin trihydrate (Exhibit B).

PRADALEX® is indicated for the treatment of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica*, *Glaesserella (Haemophilus) parasuis*, *Pasteurella multocida*, *Streptococcus suis*, and *Mycoplasma hyopneumoniae* in weaned swine intended for slaughter (nursery, growing, and finishing swine, boars intended for slaughter, barrows, gilts intended for slaughter, and sows intended for slaughter).

PRADALEX® is also indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida*, *Histophilus somni* and *Mycoplasma bovis* in cattle intended for slaughter (beef calves 2 months of age and older, growing beef steers, growing beef heifers, and beef bulls intended for slaughter), and in cattle intended for breeding less than 1 year of age (replacement beef and dairy heifers less than 1 year of age and beef and dairy bulls less than 1 year of age).

PRADALEX® is administered in the form of an injectable solution.

Pradofloxacin trihydrate has never been previously approved for commercial marketing or use in food-producing animals under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

VERAFLOX® is a product that contains the active ingredient pradofloxacin, in the form of pradofloxacin anhydrate. A copy of the product label of VERAFLOX® is attached hereto as

Exhibit D (no water molecules in the chemical formula). VERAFLOX® was previously approved on November 7, 2012 for commercial marketing or use under the Federal Food, Drug, and Cosmetic Act for use in non-food producing companion animals. For example, VERAFLOX® is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *Staphylococcus pseudintermedius*. VERAFLOX® is administered in the form of an oral suspension.

To the extent the FDA and PTO consider PRADALEX® and VERAFLOX® to contain the same active ingredient, PRADALEX® is eligible for patent term extension under 1.720(e)(3). As the MPEP states in § 2751, Section V, referring to 35 U.S.C. 156(a)(5)(C) and 37 CFR 1.720(e)(3) "[f]or animal drugs or products, **prior approval for use in a non-food producing animal will not make a patent ineligible for patent term extension based upon a later approval of the drug or product for use in food producing animals, if the later approval is the first approval of the drug or product for use in food producing animals" (emphasis added).** To the extent the drugs are considered the same by the FDA/PTO the above scenario is applicable to the present situation (*i.e.*, VERAFLOX® was approved first for non-food producing animals, PRADALEX® was subject to a separate multi-year and extensive review process, was subsequently approved, and is the first approval of the drug for use in food-producing animals).

If for some reason the FDA/PTO finds that the above situation does not apply, pradofloxacin trihydrate, the active ingredient of PRADALEX® (Exhibit B), may be considered different from pradofloxacin anhydrate, the active ingredient of VERAFLOX® (Exhibit D) for purposes of PTE. In some instances, the FDA recognizes that polymorphic/solvate forms of a drug substance (*e.g.*, anhydrate and hydrate forms) can have different chemical and physical properties that may impact drug product stability, dissolution, and bioavailability. Thus, differences in physical properties could lead to a finding that pradofloxacin trihydrate from pradofloxacin anhydrate are not the same active ingredient for purposes of PTE analysis. In that situation, PRADALEX® would be the first approval of the active ingredient pradofloxacin trihydrate, and eligible for PTE. Applicant reserves the right to present additional evidence on that issue if needed, but believes that 1.720(e)(3) applies in the first instance.

**5. A statement that the application is being submitted within the sixty day period permitted for submission pursuant to § 1.720(f) and an identification of the date of the last day on which the application could be submitted.**

PRADALEX® was approved on April 9, 2024 for commercial marketing or use. Therefore, the present application is timely filed within the sixty-day period. The last day for timely filing the present application is June 7, 2024.

**6. A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration.**

| | |
|---|---|
| Inventors: | Hubert Rast, Iris Heep, Alfons Grunenberg, Werner Hallenbach, Jordi Benet-Buchholz |
| Assignee: | ELANCO ANIMAL HEALTH GMBH (f/k/a BAYER ANIMAL HEALTH GMBH) |
| U.S. Patent No.: | 7,977,484 |
| U.S. Application No.: | 11/547,420 |
| Issue Date: | July 12, 2011 |
| Expiration Date: | August 29, 2027 |

The 20-year term of the '484 Patent under 35 U.S.C. § 154(a)(2) expires on March 19, 2025. The term of the patent was adjusted under 35 U.S.C. § 154(b) by 893 days. Therefore, the current expiration date of the '484 Patent is August 29, 2027.

**7. A copy of the patent for which an extension is being sought, including the entire specification (including claims) and drawings.**

A copy of the '484 Patent is attached hereto as Exhibit E.

**8. A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent.**

The 4th, 8th, and 12th year maintenance fees for the '484 Patent have been timely paid. Copies of the receipts showing payment of the 4th, 8th, and 12th year maintenance fees are attached hereto as Exhibit F.

No disclaimers, certificates of correction, or reexamination certificates have been submitted or issued for the '484 Patent.

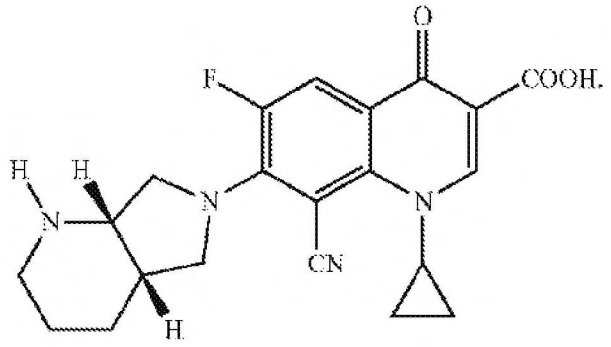
**9. A statement that the patent claims the approved product... and a showing which lists each applicable patent claim and demonstrates the manner in which at least one such patent claim reads on: (i) The approved product....**

Claims 1-3 of the '484 Patent all claim the approved product PRADALEX®.

Claim 1 of the '484 recites:

1. A pradofloxacin trihydrate of formula (II)

(II)




x 3 $H_2O$

The above formula is the same as that shown on the approved label for PRADALEX®. Accordingly, at least claim 1 of the '484 patent reads on the approved product.

Claim 2 further defines the crystal structure of the pradofloxacin trihydrate. Claim 2 recites:

2. The pradofloxacin trihydrate of claim 1, having an X-ray powder diffractogram having the reflections

| 2θ (2 theta) |
|---|
| 10.6230 |
| 14.1386 |
| 18.4032 |
| 20.9422 |
| 22.5604 |
| 22.8420 |
| 24.5165 |
| 25.8426 |
| 26.4972 |
| 26.8759 |
| 27.1231 |

of high and average intensity (>30% relative intensity). PRADALEX® contains pradofloxacin trihydrate and pradofloxacin trihydrate exhibits characteristics of the X-ray powder diffractogram of claim 2. *See also* '484 Patent at 2:30-45 (Table 1). Accordingly, claim 2 reads on the approved product.

Claim 3 further defines the crystal structure of the pradofloxacin trihydrate. Claim 3 recites:

3. The pradofloxacin trihydrate of claim 1, wherein the crystal system is monoclinic, the space group is $P2_1$, the dimensions of the unit cell are a=12.4790(18) Å α=90°, b=12.1275(18) Å β=111.009(6)°, c=15.010(2) Å γ=90°, and the volume is 2120.6(5) $Å^3$. PRADALEX® contains pradofloxacin trihydrate and pradofloxacin trihydrate exhibits the crystal structure characteristics of claim 3. *See also* '484 Patent at 2:52-60 (Table 2). Accordingly, claim 3 reads on the approved product.

**10. A statement beginning on a new page of the relevant dates and information pursuant to 35 U.S.C. 156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:**

**(ii) For a patent claiming a new animal drug:**

**(A) The date a major health or environmental effects test on the drug was initiated, and any available substantiation of that date, or the date of an exemption under subsection (j) of Section 512 of the Federal Food, Drug, and Cosmetic Act became effective for such animal drug;**

**(B) The date on which a new animal drug application (NADA) was initially submitted and the NADA number; and**

**(C) The date on which the NADA was approved.**

INAD Number (swine): 012380 (Exhibit G).

The INAD's effective date (swine): September 17, 2013.

New Animal Drug Application ("NADA") Number: 141-550 (Exhibit C).

The NADA's submission date: February 15, 2024.

The NADA's approval date: April 9, 2024.

**11. A brief description beginning on a new page of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities.**

PRADALEX® was approved by the U.S. Food and Drug Administration (the "FDA"), following submission of, *inter alia,* an INAD for swine, and a NADA.

A brief description of the significant pre-marketing regulatory activities undertaken by the Applicant during the regulatory review period applicable to this PTE application with respect to PRADALEX® and the significant dates applicable to such activities is attached hereto as Exhibit H.

**12. A statement beginning on a new page that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of extension claimed, including how the length of extension was determined.**

In the opinion of the Applicant, the '484 Patent is eligible for extension under 35 U.S.C. § 156 and 37 C.F.R. § 1.720 because it satisfies all the requirements for such an extension as follows:

A. 35 U.S.C. § 156(a) and 37 C.F.R. § 1.720(a)

The '484 Patent claims, *inter alia*, pradofloxacin trihydrate, the active ingredient of the approved product PRADALEX®.

B. 35 U.S.C. § 156(a)(1) and 37 C.F.R. § 1.720(g)

The term of the '484 Patent has not expired before the submission of this application as its expiration date is currently August 29, 2027.

C. 35 U.S.C. § 156(a)(2) and 37 C.F.R. § 1.720(b)

The term of the '484 Patent has never been extended under 35 U.S.C. § 156.

D. 35 U.S.C. § 156(a)(3) and 37 C.F.R. § 1.720(c)

This application is submitted by ELANCO ANIMAL HEALTH GMBH, the owner of the '484 Patent, in accordance with 35 U.S.C. § 156(d) and 37 C.F.R. § 1.740. This application is submitted within the sixty-day period beginning April 9, 2024 when the product received permission for commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b) and contains the information required under 35 U.S.C. § 156(d)(1).

E. 35 U.S.C. § 156(a)(4) and 37 C.F.R. § 1.720(d)

The approved product was the subject of an INAD for cattle and an INAD for swine, which became effective on June 27, 2000 and September 17, 2013, respectively. A copy of the swine INAD submission record and FDA's approval letter is attached hereto as Exhibit G. While an INAD for cattle was also submitted to the FDA, the initial studies for cattle were largely based on pradofloxacin anhydrate and took place before the issuance of the '484 Patent. Therefore, for the purpose of determining the applicable PTE for the '484 Patent, the later September 17, 2013 date related to the INAD for swine is being relied upon for the purposes of the instant PTE calculation.

The approved product was the subject of an NADA filed on February 15, 2024 and approved on April 9, 2024. Accordingly, the product was subject to a regulatory review period under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b) before its commercial marketing or use.

F. 35 U.S.C. § 156(a)(5)(C) and 37 C.F.R. § 1.720(e)(3), MPEP § 2751, Section V

The product PRADALEX® satisfies the requirements under 35 U.S.C. § 156(a)(5)(C) and 37 C.F.R. § 1.720(e)(3). This is evidenced by:

(1) The '484 Patent claims the product, pradofloxacin trihydrate.

(2) Pradofloxacin trihydrate is not covered by the claims in any other patent that has been extended.

U.S. Patent No. 6,323,213 (the "'213 Patent") was granted a PTE for the earlier approved product VERAFLOX®. However, the '213 Patent expired on or around September 7, 2021. (Exhibit I). Accordingly, the current product pradofloxacin trihydrate is not covered by the claims of the '213 Patent.[2]

(3) The term of the '484 Patent was not extended on the basis of the regulatory review period for use in non-food producing animals.

(4) The approval of PRADALEX® is the first permitted commercial marketing or use of pradofloxacin trihydrate for administration to a food-producing animal (cattle and swine); and this application is filed within the sixty-day period beginning April 9, 2024.

G. 35 U.S.C. § 156(c)(4) and 37 C.F.R. § 1.720(h)

No other patent term has been extended for the same regulatory review period for the product PRADALEX®.

H. 35 U.S.C. § 156(d)(1) and 37 C.F.R. § 1.720(f)

This application is filed within the sixty-day period beginning April 9, 2024 when PRADALEX® received permission for commercial marketing or use under § 512 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 360b).

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[2] As explained in the Federal Register, "covered by the claims" means that the drug or product would infringe a claim in the other patent. 54 Fed. Reg. 30,377 (July 20, 1989). A product cannot infringe an expired claim.

**Statement as to the Length of the Extension Claimed in Accordance with 37 C.F.R. § 1.778**

Applicant believes that the extension should be for 1,827 days (5 years), so that the expiration date for the '484 Patent shall now be August 29, 2032. The term of the extension is calculated as follows:

| | |
|---|---|
| (a) 3803 | The number of days in the period beginning on the earlier of the date a major health or environmental effects test on the drug was initiated or the date an exemption under subsection (j) of section 512 of the Federal Food, Drug, and Cosmetic Act became effective for the approved animal drug (September 17, 2013 INAD effective date) and ending on the date an application was initially submitted for such animal drug under section 512 of the Federal Food, Drug, and Cosmetic Act (February 15, 2024). (37 C.F.R. § 1.778(c)(l)) |
| (b) 54 | The number of days in the period beginning on the date the application was initially submitted for the approved animal drug under subsection (b) of section 512 of the Federal Food, Drug, and Cosmetic Act (February 15, 2024) and ending on the date such application was approved under such section (April 9, 2024). (37 C.F.R. § 1.778(c)(2)) |
| (c) 3857 | The length of the regulatory review period (the sum of (a) and (b)). (37 C.F.R. § 1.778(c)) |
| (d) 0 | The number of days in the regulatory review period that were on and before the date on which the patent was issued (July 12, 2011). (37 C.F.R. § 1.778(d)(1)(i)) |
| (e) 0* | The number of days in the regulatory review period during which it is determined under 35 U.S.C. § 156(d) by the Secretary of Health and Human Services that applicant did not act with due diligence. (37 C.F.R. § 1.778(d)(1)(ii))<br>*There has been no such determination at this time. |
| (f) 1901 | One-half the number of days remaining in the period (a) after that period is reduced in accordance with (d) and (e). (37 C.F.R. § 1.778(d)(1)(iii)) |
| (g) 1956 | Term of extension ((c) - (d) - (e) - (f)). (37 C.F.R. § 1.778(d)(1)) |
| (h) 08/29/2027 | The original term of the '484 Patent. |
| (i) 01/05/2033 | The term of the '484 Patent as extended. (37 C.F.R. § 1.778(d)(2)) |
| (j) 04/09/2038 | 14 years from the date of approval of the application under section 512 of the Federal Food, Drug, and Cosmetic Act. (37 C.F.R. § 1.778(d)(3)) |
| (k) 01/05/2033 | The earlier of (i) and (j). (37 C.F.R. § 1.778(d)(4)) |
| (l) 08/29/2032 | 5 years from the original expiration date of the '484 Patent. (37 C.F.R. § 1.778(d)(5)(i)) |
| (m) 08/29/2032 | The earlier of (k) and (l). (37 C.F.R. § 1.778(d)(5)(ii)) |

**13. A statement that applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark Office and the Secretary of Health and Human Services or the Secretary of Agriculture any information which is material to the determination of entitlement to the extension sought.**

Applicant acknowledges a duty to disclose to the Director of the United States Patent and Trademark office and the Secretary of Health and Human Services any information of which it is

aware and which is material to the determination of entitlement to the extension sought in accordance with 37 C.F.R. § 1.765.

**14. Prescribed fee.**

The prescribed fee for receiving and acting upon the application for extension is submitted herewith. The Commissioner is hereby authorized to charge Deposit Account No. 50-6936, referencing Attorney Docket No. 2920951-000297, for fees due or any deficiencies of fees and to credit any overpayments.

**15. The name, address, telephone number, and email address of the person to whom inquiries and correspondence related to the application for patent term extension are to be directed.**

David L. Vanik
McBee Moore & Vanik IP, LLC
10 South Market Street, 2nd Floor
Frederick, MD 21701
Telephone: 301-453-6100
Facsimile: 301-476-4851
Email: dvanik@mmviplaw.com

This PTE application, including its attachments and supporting papers, is being submitted via the USPTO patent electronic filing system in accordance with 37 C.F.R. § 1.740(b).

In view of the above, Applicant respectfully requests that the Commissioner grant an extension of 1,827 days (5 years) to U.S. Patent No. 7,977,484.

Favorable action is earnestly solicited.

Dated: **6 June 2024**

Respectfully submitted,

Customer No. **84331**

**McBee Moore & Vanik IP, LLC**

10 S Market St.
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Frederick, MD 21701

Telephone: 301-453-6100
Facsimile: 301-476-4851

By: /David L. Vanik/
David L. Vanik
Registration No.: 64,547

Susan E. Shaw McBee
Registration No.: 39,294

Attorneys for Applicant

# Exhibit A

# PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

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|---|---|
| SUBMISSION TYPE: | NEW ASSIGNMENT |
| NATURE OF CONVEYANCE: | ASSIGNMENT |

CONVEYING PARTY DATA

| Name | Execution Date |
|---|---|
| Hubert Rast | 10/27/2006 |
| Iris Heep | 10/16/2006 |
| Alfons Grunenberg | 09/21/2006 |
| Werner Hallenbach | 10/05/2006 |
| Jordi Benet-Buchholz | 11/16/2006 |

RECEIVING PARTY DATA

| | |
|---|---|
| Name: | Bayer HealthCare AG |
| Street Address: | 51368 |
| City: | Leverkusen |
| State/Country: | GERMAN DEMOCRATIC REPUBLIC |

PROPERTY NUMBERS Total: 1

| Property Type | Number |
|---|---|
| PCT Number: | EP0502953 |

CH $40.00 EP0502953

CORRESPONDENCE DATA

Fax Number: (203)812-6459
*Correspondence will be sent via US Mail when the fax attempt is unsuccessful.*
Phone: 203-812-2712
Email: gil.cunha.b@bayer.com
Correspondent Name: William F. Gray
Address Line 1: Bayer Pharmaceuticals Corporation
Address Line 2: 400 Morgan Lane
Address Line 4: West Haven, CONNECTICUT 06516

| | |
|---|---|
| ATTORNEY DOCKET NUMBER: | BHC 031064 |
| NAME OF SUBMITTER: | William F. Gray |

Total Attachments: 1

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# Assignment

For valuable consideration, the receipt and adequacy of which is hereby acknowledged,

I/We

1)RAST, Hubert 2)HEEP, Iris 3)GRUNENBERG, Alfons
4)HALLENBACH, Werner 5)BENET-BUCHHOLZ, Jordi

1)Auf dem Bruch 77a, 51381 Leverkusen, Germany
2)Grüner Weg 7a, 50859 Köln, Germany
3)Gneisenaustr. 15, 41539 Dormagen, Germany
4)Lichtenbergerstr. 68, 40789 Monheim, Germany
5)Placa Romani 3A, 43893 Altafulla, Spain

hereby sell, assign, and transfer unto **Bayer HealthCare AG** a corporation of **Germany** located at **51368 Leverkusen, Germany** the entire right, title, and interest in and to my/our application for Letters Patent of the United States, executed concurrently herewith, entitled

**NOVEL CRYSTALLINE FORM OF 8-CYANO-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID**

**Filed: March 19, 2005** **PCT-Serial No.: PCT/EP2005/002953**

and my/our entire right, title, and interest in and to all my/our inventions, whether joint or sole, disclosed in said application for Letters Patent, and in and to all divisional or continuation applications that may be filed for United States Letters Patent for any of said inventions, and in and to all patents that may be granted on the foregoing applications, and I/we hereby agree, whenever requested, to communicate to said assignee, its successors and assigns, any facts known to my/us respecting said inventions and to execute all applications or papers necessary to obtain and maintain proper patent protection on said inventions in the United States.

| Date/Datum | Inventor(s)/Erfinder |
|---|---|
| 2006-10-27 | 1. Hubert Rast |
| 2006-10-16 | 2. Iris Heep |
| 2006-09-21 | 3. Grunenberg Alfons |
| 2006-10-05 | 4. Werner Hallenbach |
| 2006-11-16 | 5. |

BHC 03 1064-US

# PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

| | |
|---|---|
| SUBMISSION TYPE: | NEW ASSIGNMENT |
| NATURE OF CONVEYANCE: | ASSIGNMENT |

CONVEYING PARTY DATA

| Name | Execution Date |
|---|---|
| BAYER HEALTHCARE AG | 12/04/2008 |

RECEIVING PARTY DATA

| | |
|---|---|
| Name: | BAYER ANIMAL HEALTH GMBH |
| Street Address: | LAW AND PATENTS |
| Internal Address: | BUILDING Q 18 |
| City: | LEVERKUSEN |
| State/Country: | GERMANY |
| Postal Code: | 66201 |

PROPERTY NUMBERS Total: 26

| Property Type | Number |
|---|---|
| Application Number: | 10576408 |
| Application Number: | 10682555 |
| Application Number: | 11547420 |
| Application Number: | 10585608 |
| Application Number: | 11451676 |
| Application Number: | 10593537 |
| Application Number: | 11587480 |
| Application Number: | 11631089 |
| Application Number: | 11813354 |
| Application Number: | 11721204 |
| Application Number: | 11718999 |
| Application Number: | 11718914 |
| Application Number: | 11719379 |
| Application Number: | 11574955 |

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|---|---|
| Application Number: | 11574953 |
| Application Number: | 11817531 |
| Application Number: | 11908309 |
| Application Number: | 11995995 |
| Application Number: | 11721209 |
| Application Number: | 10516344 |
| Application Number: | 10541087 |
| Application Number: | 10555298 |
| Application Number: | 10562324 |
| Application Number: | 10559995 |
| Application Number: | 10567057 |
| Application Number: | 11574957 |

CORRESPONDENCE DATA


Fax Number: (913)268-2889

*Correspondence will be sent via US Mail when the fax attempt is unsuccessful.*

Phone: 913-268-2038

Email: jessica.monachello.b@bayer.com

Correspondent Name: Jessica Monachello

Address Line 1: P.O. Box 390

Address Line 4: Shawnee Mission, KANSAS 66201


| | |
|---|---|
| ATTORNEY DOCKET NUMBER: | BAYER HEALTHCARE AG ASSIG |
| NAME OF SUBMITTER: | JESSICA MONACHELLO |

Total Attachments: 4
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UNITED STATES PATENT ASSIGNMENT

WHEREAS, Bayer HealthCare AG, 51368 Leverkusen, Germany, a corporation organized under the laws of Germany (hereinafter referred to as "ASSIGNOR"), owns the following inventions (the "INVENTIONS") entitled:

- PHARMACEUTICAL FORMULATIONS CONTAINING FLAVORING SUBSTANCES WITH IMPROVED PHARMACEUTICAL PROPERTIES and has executed an application for a United States patent based thereon (serial number 10/576,408, filed on April 18, 2006); 07/1062-03
- 18-MEMBERED NITROBENZYL-AND AMINOBENZYL-SUBSTITUTED CYCLOHEXADEPSIPEPTIDES FOR CONTROLLING ENDOPARASITES AND A PROCESS FOR THER PREPARATION and has executed an application for a United States patent based thereon (serial number 10/582,555, filed on June 9, 2006); 07/1061-03
- NEW CRYSTALLINE FORM OF 8-CYANO-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINECARBOXYLIC ACID and has executed an application for a United States patent based thereon (serial number 11/547,420, filed on September 29, 2006); 07/1062-03
- TOPICALLY APPLIED MEDICAMENT FOR ANIMALS and has executed an application for a United States patent based thereon (serial number 10/585,808, filed on July 10, 2006); 07/1082-03
- ENDOPARASITICIDAL COMPOSITIONS FOR TOPICAL APPLICATION and has executed an application for a United States patent based thereon (serial number 11/451,676, filed on June 13, 2006); 07/1070-03
- PARASITICIDAL COMPOSITIONS and has executed an application for a United States patent based thereon (serial number 10/593,537, filed on September 19, 2006); 07/1088-03
- DERMALLY APPLICABLE LIQUID FORMULATIONS FOR CONTROLLING PARASITIC ARTHROPODS ON ANIMALS and has executed an application for a United States patent based thereon (serial number 11/587,480, filed on October 25, 2006); 07/1081-03
- ACTIVE SUBSTANCE-CONTAINING SOLID SHAPED BODIES FOR EXTERNAL USE AGAINST PARASITES IN ANIMALS and has executed an application for a United States patent based thereon (serial number 11/631,089, filed on December 28, 2006); 07/1092-03
- SUBSTITUTED BENZIMIDAZOLES FOR TREATMENT OF HISTOMONIASIS and has executed an application for a United States patent based thereon (serial number 11/813,354, filed on July 5, 2007); 07/1221-03

- MEDICAMENT FOR HYGIENIC APPLICATION INSIDE THE EAR and has executed an application for a United States patent based thereon (serial number 11/721,204, filed on June 8, 2007);
- TREATMENT OF MASTITIS and has executed an application for a United States patent based thereon (serial number 11/718,999, filed on May 10, 2007);
- ANTI-DEMODICOSIS AGENT and has executed an application for a United States patent based thereon (serial number 11/718,914, filed on May 8, 2007);
- PREVENTING VERTICAL ENDOPARASITE INFECTIONS and has executed an application for a United States patent based thereon (serial number 11/719,379, filed on May 15, 2007);
- PHARMACEUTICAL COMPOSITION and has executed an application for a United States patent based thereon (serial number 11/574,955, filed on March 8, 2007);
- PHARMACEUTICAL COMPOSITION and has executed an application for a United States patent based thereon (serial number 11/574,953, filed on August 27, 2007);
- REDUCTION OF DIGESTIBILITY OF PHOSPHORUS and has executed an application for a United States patent based thereon (serial number 11/817,531, filed on August 31, 2007);
- ENDOPARASITICIDAL COMPOSITIONS and has executed an application for a United States patent based thereon (serial number 11/908,309, filed on September 11, 2007);
- DISINFECTANT and has executed an application for a United States patent based thereon (serial number 11/995,995, filed on January 17, 2008);
- STABILIZATION OF GLUCOCORTICOID ESTERS WITH ACIDS and has executed an application for a United States patent based thereon (serial number 11/721,209, filed on June 8, 2007);
- PHARMACEUTICAL PREPARATION FOR ORAL ADMINISTRATION CONTAINING ION-EXCHANGE RESINS LOADED WITH ACTIVE INGREDIENTS AND INTRINSICALLY VISCOUS GELLING AGENTS AS THICKENING AGENTS and has executed an application for a United States patent based thereon (serial number 10/516,344, filed on November 21, 2005);
- REPELLENT and has executed an application for a United States patent based thereon (serial number 10/541,087, filed on April 10, 2006);
- COMPOSITIONS FOR CONTROLLING PARASITES ON ANIMALS and has executed an application for a United States patent based thereon (serial number 10/555,298, filed on November 2, 2005);

- USE OF A NOVEL EIMERIA GENE AND CORRESPONDING PROTEIN and has executed an application for a United States patent based thereon (serial number 10/562,324, filed on June 29, 2006); 7697-US
- TABLETS CONTAINING ENROFLOXACIN AND FLAVOURING AGENTS AND/OR FLAVOURS and has executed an application for a United States patent based thereon (serial number 10/559,995, filed on December 8, 2005); 36 780-US
- NOVEL USE OF QUINOLONE ANTIBIOTICS and has executed an application for a United States patent based thereon (serial number 10/567,057, filed on June 28, 2006); 36 849-US
- PHARMACEUTICAL COMPOSITION IN THE FORM OF A WATER SOLUBLE SOLID DOSAGE FORM and has executed an application for a United States patent based thereon (serial number 11/574,937, filed on March 8, 2007); 04 1 769-US

collectively (the "APPLICATIONS")

AND, WHEREAS, Bayer Animal Health GmbH, 51368 Leverkusen, Germany, a corporation organized under the laws of Germany (hereinafter referred to as "ASSIGNEE"), is desirous of acquiring certain rights thereunder;

NOW, THEREFORE, for one dollar and other good and valuable consideration, receipt of all of which is hereby acknowledged, ASSIGNOR has agreed to and does hereby sell, assign, and transfer unto said ASSIGNEE the entire right, title and interest in and throughout the United States of America (including its territories and dependencies) to said INVENTIONS, said APPLICATIONS, any other United States application (including divisional, continuing, or reissue applications) based in whole or in part on said APPLICATIONS or in whole or in part on said INVENTIONS;

TO BE HELD AND ENJOYED by said ASSIGNEE, its successors and assigns, as fully and entirely as the same would have been held and enjoyed by ASSIGNOR had no sale and assignment of said interest been made;

AND ASSIGNOR hereby authorizes and requests the Commissioner of Patents of the United States of America to issue any and all United States patents which may be granted upon said United States applications or any of them, or upon said INVENTIONS or any part thereof, to said ASSIGNEE;

AND ASSIGNOR, his successors and assigns, hereby agrees to execute without further consideration any further lawful documents and any further assurances, and any divisional, continuing, reissue, or other applications for patents of any country, that may be deemed necessary by said ASSIGNEE fully to secure to said ASSIGNEE its interest as aforesaid in and to said INVENTIONS or any part thereof, and in and to said several patents or any of them;

AND ASSIGNOR hereby covenants and agrees with said ASSIGNEE, its successors and assigns, that ASSIGNOR has granted no right or license to make, use, or sell said INVENTIONS, to anyone except said ASSIGNEE, that prior to the execution of this assignment, ASSIGNOR'S right, title and interest in said INVENTIONS have not been otherwise encumbered, and that ASSIGNOR has not executed and will not execute any instrument in conflict herewith.

Signature

Dr. S. Beyreather (secretary)
Printed Name and Title

December 9, 2008
Date

Signature

Dr. F. Burkert (secretary)

Dr. J. Thomaier (secretary)
Printed Name and Title

December 9, 2008
Date

Dr. F. Kohler (secretary)

# PATENT ASSIGNMENT

Electronic Version v1.1
Stylesheet Version v1.1

| | |
|---|---|
| SUBMISSION TYPE: | NEW ASSIGNMENT |
| NATURE OF CONVEYANCE: | ASSIGNMENT |

CONVEYING PARTY DATA

| Name | Execution Date |
|---|---|
| Bayer Animal Health GmbH | 04/01/2012 |

RECEIVING PARTY DATA

| | |
|---|---|
| Name: | Bayer Intellectual Property GmbH |
| Street Address: | Alfred-Nobel-Strasse 10 |
| Internal Address: | Building 4865 |
| City: | Monheim |
| State/Country: | GERMANY |
| Postal Code: | 40789 |

PROPERTY NUMBERS Total: 51

| Property Type | Number |
|---|---|
| Application Number: | 10576408 |
| Application Number: | 12949833 |
| Application Number: | 10582555 |
| Application Number: | 11547420 |
| Application Number: | 11451676 |
| Application Number: | 11631089 |
| Application Number: | 11721204 |
| Application Number: | 12280448 |
| Application Number: | 11718914 |
| Application Number: | 11908309 |
| Application Number: | 11721209 |
| Application Number: | 12954989 |
| Application Number: | 12442680 |
| Application Number: | 12280996 |

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|---|---|
| Application Number: | 12377156 |
| Application Number: | 12520169 |
| Application Number: | 12520552 |
| Application Number: | 13282588 |
| Application Number: | 12951581 |
| Application Number: | 12602002 |
| Application Number: | 12676668 |
| Application Number: | 12739873 |
| Application Number: | 12990389 |
| Application Number: | 13000871 |
| Application Number: | 12922137 |
| Application Number: | 13000715 |
| Application Number: | 13000510 |
| Application Number: | 13132872 |
| Application Number: | 13147088 |
| Application Number: | 13202739 |
| Application Number: | 08849259 |
| Application Number: | 09435271 |
| Application Number: | 08011599 |
| Application Number: | 10290827 |
| Application Number: | 09125191 |
| Application Number: | 09718062 |
| Application Number: | 10613819 |
| Application Number: | 09601572 |
| Application Number: | 10347003 |
| Application Number: | 11871302 |
| Application Number: | 10311419 |
| Application Number: | 10362038 |
| Application Number: | 10682127 |
| Application Number: | 10616344 |
| Application Number: | 11243293 |
| Application Number: | 10541087 |
| Application Number: | 10555298 |
| Application Number: | 10559995 |
| Application Number: | 10567057 |

| | |
|---|---|
| | 13394529 |
| Application Number: | 13320289 |

CORRESPONDENCE DATA

| | |
|---|---|
| Fax Number: | 9132682071 |
| *Correspondence will be sent via US Mail when the fax attempt is unsuccessful.* | |
| Phone: | 9132682038 |
| Email: | jessica.monachello@bayer.com |
| Correspondent Name: | Bayer HealthCare LLC |
| Address Line 1: | PO Box 390 |
| Address Line 4: | Shawnee Mission, KANSAS 66201 |

| | |
|---|---|
| NAME OF SUBMITTER: | JESSICA MONACHELLO |

Total Attachments: 2
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# ASSIGNMENT DEED

For and in consideration of the amount of USD $1.00 (one US Dollar) and other good and valuable consideration, the receipt and sufficiency is hereby acknowledged,

ASSIGNOR, **Bayer Animal Health GmbH**, a corporation organized under the laws of the Federal Republic of Germany, and located at D-51368 Leverkusen, Germany,

hereby sells, assigns and transfers its entire worldwide ownership, right, title and interest in and to the Patents and Patent Applications listed on the attached Schedule A, and all patents granted thereon or claiming priority thereto or claiming common priority therewith, including all foreign counterparts, substitutions, divisions, continuations, continuations-in-part, reissues, reexaminations or extensions of any of such patent applications or patents, and respective supplementary protection certificates, effective as of April 1, 2012, to

ASSIGNEE, **Bayer Intellectual Property GmbH**, a corporation organized under the laws of the Federal Republic of Germany, and located at Creative Campus Monheim, Building 4865, Alfred-Nobel-Straße 10, 40789 Monheim,

hereby accepts the entire worldwide right, title and interest of **Bayer Animal Health GmbH** in and to the Patents and Patent Applications listed on the attached Schedule A, and all Patents and Patent Applications claiming priority thereto or claiming common priority therewith, including all foreign counterparts, substitutions, divisions, continuations, continuations-in-part, reissues, reexaminations or extensions of any of such Patents or Patents Applications, and respective supplementary protection certificates, effective as of April 1, 2012.

IN WITNESS WHEREOF, we have hereunto respectively set our hands and seal on the date(s) shown below:

For **Bayer Animal Health GmbH**

| | |
|---|---|
| Signature | Signature |
| Dr. Frank Burkert | |
| Name | Name |
| authorized officer | |
| Title | Title |

For **Bayer Intellectual Property GmbH**

| | |
|---|---|
| Signature | Signature |
| Kai Kammerath | |
| Name | Name |
| authorized officer | |
| Title | Title |

# SCHEDULE A

Patents and Patent Applications Transferred

| File | Application Date | Application Number | Issue Date | Patent Number |
|---|---|---|---|---|
| BHC031062 PCT-US | 30.10.2004 | 10/576408 | 28.12.2010 | 7858120 |
| BHC031062 PCT-US01 | 19.11.2010 | 12/949533 | | |
| BHC031063 PCT-US | 06.12.2004 | 10/582555 | 12.01.2010 | 7645738 |
| BHC031064 PCT-US | 19.03.2008 | 11/547420 | 12.07.2011 | 7977484 |
| BHC031090 PCT-US | 30.11.2004 | 11/461676 | 27.07.2010 | 7763583 |
| BHC041182 PCT-US | 16.06.2005 | 11/631069 | 22.03.2011 | 7910122 |
| BHC041276 PCT-US | 03.12.2005 | 11/721204 | | |
| BHC041317 PCT-US | 23.02.2007 | 12/280448 | | |
| BHC041336 PCT-US | 27.10.2006 | 11/718914 | | |
| BHC051031 PCT-US | 27.02.2005 | 11/908309 | | |
| BHC051135 PCT-US | 03.12.2005 | 11/721209 | | |
| BHC051135 PCT-US01 | 29.11.2010 | 12/954989 | | |
| BHC051155 PCT-US | 06.10.2007 | 12/442680 | | |
| BHC061005 PCT-US | 23.02.2007 | 12/280996 | | |
| BHC061142 PCT-US | 06.06.2007 | 12/377156 | | |
| BHC061176 PCT-US | 14.12.2007 | 12/520169 | | |
| BHC061177 PCT-US | 14.12.2007 | 12/520552 | 06.12.2011 | 8071116 |
| BHC061177 PCT-US01 | 27.10.2011 | 13/282588 | | |
| BHC071012 US01 | 22.11.2010 | 12/951581 | | |
| BHC071041 PCT-US | 26.06.2008 | 12/602002 | | |
| BHC071077 PCT-US | 26.08.2008 | 12/676568 | 27.03.2012 | 8143411 |
| BHC071086 PCT-US | 12.11.2008 | 12/739873 | | |
| BHC081003 PCT-US | 23.04.2009 | 12/990389 | | |
| BHC081006 PCT-US | 20.06.2009 | 13/000871 | | |
| BHC081011 PCT-US | 28.02.2009 | 12/922137 | | |
| BHC081012 PCT-US | 20.06.2009 | 13/000715 | | |
| BHC081013 PCT-US | 16.06.2009 | 13/000510 | | |
| BHC088006 PCT-US | 24.11.2009 | 13/132872 | | |
| BHC091042 PCT-US | 06.09.2010 | PCT/EP2010/063016 | | |
| BHC097001 PCT-US01 | 19.01.2010 | 13/147098 | | |
| BHC097002 PCT-US01 | 07.05.2010 | PCT/EP2010/002809 | | |
| BHC098001 PCT-US | 05.03.2010 | 13/202739 | | |
| LEA 30763 US | 27.11.1995 | 08/849259 | 14.12.1999 | 6001858 |
| LEA 30763 US01 | 05.11.1999 | 09/435271 | 16.04.2002 | 6372765 |
| LEA 31247 US | 30.07.1996 | 08/011599 | | |
| LEA 31247 US01 | 08.11.2002 | 10/290827 | 10.08.2010 | 7772190 |
| LEA 31592 US | 12.02.1997 | 09/125191 | 27.11.2001 | 6323213 |
| LEA 31592 US01 | 21.11.2000 | 09/716052 | 21.08.2001 | 6276013 |
| LEA 31923 US01 | 03.07.2003 | 10/613819 | | |
| LEA 32803 US | 10.02.1999 | 09/601572 | 09.04.2002 | 6369054 |
| LEA 32804 US01 | 17.01.2003 | 10/347003 | 10.06.2008 | 7384938 |
| LEA 34114 US01 | 12.10.2007 | 11/871302 | | |
| LEA 34267 US | 18.06.2001 | 10/311419 | 29.03.2011 | 7914816 |
| LEA 34648 US | 06.08.2001 | 10/362039 | 29.03.2011 | 7915257 |
| LEA 35172 US | 02.04.2002 | 10/682127 | 01.06.2010 | 7728011 |
| LEA 36165 US | 19.05.2003 | 10/516344 | | |
| LEA 36367 US | 06.03.2004 | 11/243293 | | |
| LEA 36544 US | 05.01.2004 | 10/541087 | | |
| LEA 36676 US | 24.04.2004 | 10/555298 | 17.01.2012 | 8097603 |
| LEA 36780 US | 14.06.2004 | 10/559986 | | |
| LEA 36807 PCT-US | 02.08.2004 | 10/567057 | | |

# PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

Assignment ID: PATI13168

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|---|---|
| SUBMISSION TYPE: | NEW ASSIGNMENT |
| NATURE OF CONVEYANCE: | CHANGE OF NAME |

**CONVEYING PARTY DATA**

| Name | Execution Date |
|---|---|
| Bayer Animal Health GmbH | 04/04/2023 |

**RECEIVING PARTY DATA**

| | |
|---|---|
| Company Name: | Elanco Animal Health GmbH |
| Street Address: | Alfred-Nobel-Strasse 50 |
| City: | Monheim am Rhein |
| State/Country: | GERMANY |
| Postal Code: | 40789 |

**PROPERTY NUMBERS Total: 65**

| Property Type | Number |
|---|---|
| Application Number: | 11871302 |
| Application Number: | 16498674 |
| Application Number: | 15033464 |
| Application Number: | 15033415 |
| Application Number: | 14113778 |
| Application Number: | 14862103 |
| Application Number: | 14824145 |
| Application Number: | 14808425 |
| Application Number: | 14360713 |
| Application Number: | 13878901 |
| Application Number: | 13390302 |
| Application Number: | 13282588 |
| Application Number: | 13147088 |
| Application Number: | 12951581 |
| Application Number: | 12676568 |
| Application Number: | 12520552 |
| Application Number: | 12442680 |
| Application Number: | 12280448 |
| Application Number: | 11718914 |
| Application Number: | 11631089 |

| Property Type | Number |
|---|---|
| Application Number: | 11547420 |
| Application Number: | 10682127 |
| Application Number: | 10576408 |
| Application Number: | 10567057 |
| Application Number: | 10555298 |
| Application Number: | 10516344 |
| Application Number: | 18057053 |
| Application Number: | 17995750 |
| Application Number: | 17916195 |
| Application Number: | 17908194 |
| Application Number: | 17795652 |
| Application Number: | 17766151 |
| Application Number: | 17466863 |
| Application Number: | 17053680 |
| Application Number: | 16624117 |
| Application Number: | 16776377 |
| Application Number: | 16776374 |
| Application Number: | 16762068 |
| Application Number: | 16757083 |
| Application Number: | 16716205 |
| Application Number: | 16636276 |
| Application Number: | 16608744 |
| Application Number: | 16484670 |
| Application Number: | 16348797 |
| Application Number: | 16320256 |
| Application Number: | 16093565 |
| Application Number: | 16074289 |
| Application Number: | 16058888 |
| Application Number: | 14916244 |
| Application Number: | 14891762 |
| Application Number: | 15962414 |
| Application Number: | 15571650 |
| Application Number: | 15504294 |
| Application Number: | 15325665 |
| Application Number: | 15318967 |
| Application Number: | 15313343 |
| Application Number: | 15109630 |
| Application Number: | 15037564 |

| Property Type | Number |
|---|---|
| Application Number: | 15037402 |
| Application Number: | 15033928 |
| Application Number: | 15022583 |
| Application Number: | 14653676 |
| Application Number: | 14633920 |
| Application Number: | 14414254 |
| Application Number: | 14407455 |

CORRESPONDENCE DATA


Fax Number: 7166260366

***Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.***

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Email: esimpson@colsonlawgroup.com
Correspondent Name: Ellen S. Simpson
Address Line 1: Colson Law Group
Address Line 2: 5555 Main Street
Address Line 4: Buffalo, NEW YORK 14221


| | |
|---|---|
| ATTORNEY DOCKET NUMBER: | BPN0011 |
| NAME OF SUBMITTER: | ELLEN SIMPSON |
| SIGNATURE: | ELLEN SIMPSON |
| DATE SIGNED: | 02/08/2024 |

Total Attachments: 4

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source=Notarized_EN_ECR_EAH_Short Version_CON Effective Date 04.04.23_Legalized by Apostille_ECR_EN translation#page3.tif

Commercial Register B of the District Court Köln | Imprint | Number of the firm: **HRB 52145**
Retrieval of May 3, 2023 11:01 | Page 1 of 15

| Entry No. | a) Firm name<br>b) Seat, establishment, domestic business address, authorized recipient, branch establishments<br>c) Purpose of the enterprise | Share or nominal capital | a) General rules of representation<br>b) Management board, management organ, managing directors, general partners, managers, authorized representatives and special powers of representation | Prokura | a) Legal form, commencement, articles of association or shareholders' agreement<br>b) Other legal relationships | a) Date of entry<br>b) Remarks |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1-3 | ... | ... | ... | ... | ... | ... |
| 4 | a)<br>Bayer Animal Health GmbH<br><br>c)<br>... | | | ... | a)<br>On March 20, 2008, the shareholders' meeting adopted a resolution amending the company name and, accordingly, the shareholders' agreement in § 1, and also the purpose of the enterprise and, accordingly, the shareholders' agreement in § 3. The shareholders' agreement was reworded. | a)<br>March 31, 2008<br>Keusch |
| 5-79 | ... | ... | ... | ... | ... | ... |
| 80 | a)<br>Elanco Animal Health GmbH | | | | a)<br>The shareholders' meeting of January 10, 2023 adopted a resolution amending the shareholders' agreement in § 1 (company name) and thereby the company name. | a)<br>March 31, 2023<br>Asmussen |
| 81 | ... | ... | ... | ... | ... | ... |

Partially translated on the basis of the extract from the Commercial Register of the District Court Köln, historical printout, HRB 52145, retrieved on May 3, 2023, 11:01 am.

Bremen, May 3, 2023

[Malte Nentwig]

MORNINGSIDE

# TRANSLATOR CERTIFICATION

Date: November 14, 2023

To whom it may concern:

I, Kim Tanneberger , a translator fluent in the German and English languages, on behalf of Morningside Translations, do solemnly and sincerely declare that the following is, to the best of my knowledge and belief, a true and correct translation of the document(s) listed below in a form that best reflects the intention and meaning of the original text.

The document is designated as:
**Source: ECR_EAH_Short Version_CON Effective Date 04.04.23_Legalized by Apostille_ECR without history.pdf**

**Target: EN_ECR_EAH_Short Version_CON Effective Date 04.04.23_Legalized by Apostille_ECR without history - English Translation - changes & comment**

Signature

Kim Tanneberger
Print

AFFIRMED BEFORE ME THIS
15TH DAY OF NOVEMBER 2023
NOTARY PUBLIC

CLIFFORD MORRIS
Notary Public
1 London Road, Southampton
Hampshire, SO15 2AE, England
+44(0)7736 110542
cliff.morris@parissmith.co.uk

# NOTARIAL CERTIFICATE

Upon today's inspection of the electronic retrieval from the commercial register of the local court of Duesseldorf under registry number HRB 100426 I hereby certify that the following printout is a correct and complete reproduction of the content of the electronic retrieval.

Monheim am Rhein, August 29, 2023

Dr. Jens Hennig, Civil Law Notary

[illegible] register B of the Local Court Düsseldorf **Print out** Number of the company: **HRB 1004**[illegible]

Retrieval dated 08.29.2023 11:05AM Page 1 of 1

| Number of the entry | a) Company name<br>b) Registered office, branch office, domestic business address, authorized recipient, subsidiaries<br>c) Object of the company | Share capital or nominal capital | a) General representation regulations<br>b) Management board, management body, managing directors, personally liable partner, managing director, authorized representatives and special power of representation | Procuration | a) Legal form, commencement, articles of association or partnership agreement<br>b) Other legal relationships | a) Date of entry<br>b) Remarks |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 1 | a)<br>Elanco Animal Health GmbH<br><br>b)<br>Monheim am Rhein<br>Business address:<br>Alfred-Nobel-Straße 50, 40789 Monheim am Rhein<br><br>c)<br>Distribution, other industrial activity or provision of services in the field of animal health and animal care. | 25,000.00 EUR | a)<br>If only one managing director has been appointed, they shall represent the company alone. If several managing directors have been appointed, the company shall be represented by two managing directors or by one managing director together with an authorized signatory.<br><br>b) Managing director:<br>Dr. Bongaerts, Sabine, Dormagen, *11.14.1968<br>authorized to act as sole representative with the authority to conclude legal transactions in the name of a third party.<br><br>Managing Director:<br>Vehling, Liska, Düsseldorf, *03.09.1977<br>authorized to act as sole representative with the authority to conclude legal transactions in the name of a third party. | Individual power of representation:<br>Dr. Laber-Probst, Birgit, Cologne, *05.28.1966<br>Riedel, Dirk, Leverkusen, *03.04.1964<br>Dr. Stanneck, Dorothee, Solingen, *05.12.1967<br>Dr. Storch, Matthias, Leverkusen, *07.04.1961<br>Felten, Julia, Cologne, *11.19.1981<br>Krebsfänger, Niels, Cologne, *01.11.1972<br>Stölting, Jörn, Cologne, *04.30.1967<br>Puschmann, Stefan, Leverkusen, *03.18.1974<br>Kettner, Andrea, Cologne, *11.12.1974<br>Dr. Mertens, Christina Maria, Essen, *06.21.1967<br>Dr. Hehmann, Marc, Langenfeld, *09.16.1974<br>Wichmann, Cindy, Butzbach, *10.15.1987 | a)<br>Limited liability company<br>Articles of association dated 12.09.2003, subsequently amended. The shareholders' meeting on 01.10.2023 amended the Articles of Association in Section 2 and with it the relocation of the registered office from Leverkusen (previously Cologne Local Court HRB 52145) to Monheim am Rhein.<br><br>b)<br><br>A profit and loss transfer agreement was made with Elanco GmbH, Cuxhaven (Tostedt Local Court, HRB 206619), as the controlling company on 08.10.2020. It was approved by the shareholders' meeting on 08.11.2020. | a)<br>04.04.2023<br>Sönnichsen |
| 2 | | | b)<br>No longer managing director:<br>Dr. Bongaerts, Sabine, Dormagen, *11.14.1968 | | | a)<br>08.23.2023<br>Kronz |

# PATENT ASSIGNMENT COVER SHEET

Electronic Version v1.1
Stylesheet Version v1.2

Assignment ID: PATI10512

| | |
|---|---|
| SUBMISSION TYPE: | NEW ASSIGNMENT |
| NATURE OF CONVEYANCE: | NUNC PRO TUNC ASSIGNMENT |
| EFFECTIVE DATE: | 09/01/2019 |

**CONVEYING PARTY DATA**

| Name | Execution Date |
|---|---|
| Bayer Intellectual Property GmbH | 01/18/2024 |

**RECEIVING PARTY DATA**

| | |
|---|---|
| Company Name: | Bayer Animal Health GmbH |
| Street Address: | Kaiser-Wilhelm-Allee 20 |
| City: | Leverkusen |
| State/Country: | GERMANY |
| Postal Code: | 51373 |

**PROPERTY NUMBERS Total: 23**

| Property Type | Number |
|---|---|
| Application Number: | 14113778 |
| Application Number: | 14862103 |
| Application Number: | 14824145 |
| Application Number: | 14808425 |
| Application Number: | 14360713 |
| Application Number: | 13878901 |
| Application Number: | 13390302 |
| Application Number: | 13282588 |
| Application Number: | 13147088 |
| Application Number: | 12951581 |
| Application Number: | 12676568 |
| Application Number: | 12520552 |
| Application Number: | 12442680 |
| Application Number: | 12280448 |
| Application Number: | 11718914 |
| Application Number: | 11631089 |
| Application Number: | 11547420 |
| Application Number: | 10682127 |
| Application Number: | 10576408 |

| Property Type | Number |
|---|---|
| Application Number: | 10567057 |
| Application Number: | 10555298 |
| Application Number: | 10516344 |
| Application Number: | 11871302 |

CORRESPONDENCE DATA

Fax Number: 7166260366

*Correspondence will be sent to the e-mail address first; if that is unsuccessful, it will be sent using a fax number, if provided; if that is unsuccessful, it will be sent via US Mail.*

Phone: 7162394300
Email: esimpson@colsonlawgroup.com
Correspondent Name: Ellen S. Simpson
Address Line 1: Colson Law Group
Address Line 2: 5555 Main Street
Address Line 4: Buffalo, NEW YORK 14221

| | |
|---|---|
| ATTORNEY DOCKET NUMBER: | BPN0011 |
| NAME OF SUBMITTER: | ELLEN SIMPSON |
| SIGNATURE: | ELLEN SIMPSON |
| DATE SIGNED: | 02/07/2024 |

Total Attachments: 2
source=BIP-BAH_588 EAH_Nunc pro Tunc DoA_BIP_BAH_EN_US_PTs_SIGNED#page1.tif
source=BIP-BAH_588 EAH_Nunc pro Tunc DoA_BIP_BAH_EN_US_PTs_SIGNED#page2.tif

# Nunc Pro Tunc Assignment Agreement
# and
# Consent to Recordal
# United States

THIS DEED is made between:

Bayer Intellectual Property GmbH, a company duly organized and existing under the Laws of Germany, of Alfred-Nobel-Strasse 50, 40789 Monheim am Rhein, Germany
("the Assignor");

and

Bayer Animal Health GmbH, a company duly organized and existing under the Laws of Germany, of Kaiser-Wilhelm-Allee 20, 51373Leverkusen, Germany, now known as Elanco Animal Health GmbH
("the Assignee");

WHEREAS:

(a) Assignor, was the proprietor of the patents in United States as set out in the attached schedule marked Annex A;

(b) Assignor and Assignee have agreed that patents listed in the attached schedule "Annex A" should be transferred to the Assignee,

(c) This Assignment is made and effective as of September 1st, 2019 by Assignor conveying rights to Assignee on that date; and

IT IS AGREED THAT:

For good and valuable consideration, receipt of which is hereby acknowledged by the Assignor, the Assignor hereby assigns, transfers and sets over unto the Assignee, its successors and assigns all rights, title and interests in United States in the patents together with the goodwill of the business represented and symbolised by the patents and the Assignee accepts the said assignment.

IN WITNESS WHEREOF, the Assignor and Assignee have caused this Assignment to be executed by their authorized representatives.

Signed as a Deed in Munich on behalf of the Assignor this 18th day of January 2024 by

Michal Molcan, Proxy-Holder of
Bayer Intellectual Property GmbH

Signed as a Deed in Munich on behalf of the Assignee this 18th day of January 2024 by

Juliane Weiß, Proxy-Holder of
Elanco Animal Health GmbH

Annex A

| Patent Title | Application No. | Grant No. |
|---|---|---|
| Patent Title unknown/ not available | 14/113778 | 9307764 |
| Patent Title unknown/ not available | 14/862103 | 9609871 |
| Patent Title unknown/ not available | 14/824145 | 9801355 |
| Patent Title unknown/ not available | 14/808425 | 9610297 |
| Patent Title unknown/ not available | 14/360713 | 9593140 |
| Patent Title unknown/ not available | 13/878,901 | 9744127 |
| Patent Title unknown/ not available | 13/390302 | 9227923 |
| Patent Title unknown/ not available | 13/282588 | 9137995 |
| Patent Title unknown/ not available | 13/147088 | 9137989 |
| Patent Title unknown/ not available | 12/951581 | 9089582 |
| Patent Title unknown/ not available | 12/676568 | 8143411 |
| Patent Title unknown/ not available | 12/520552 | 8071116 |
| Patent Title unknown/ not available | 12/442680 | 8497377 |
| Patent Title unknown/ not available | 12/280448 | 10231925 |
| Patent Title unknown/ not available | 11/718914 | 9662309 |
| Patent Title unknown/ not available | 11/631089 | 7910122 |
| Patent Title unknown/ not available | 11/547420 | 7977484 |
| Patent Title unknown/ not available | 10/682127 | 7728011 |
| Patent Title unknown/ not available | 10/576408 | 7858120 |
| Patent Title unknown/ not available | 10/567057 | 8658645 |
| Patent Title unknown/ not available | 10/555298 | 8097603 |
| Patent Title unknown/ not available | 10/516344 | 8545829 |
| Patent Title unknown/ not available | 11/871302 | 9399037 |

# Exhibit B

7.875 in

9.8125 in

Elanco™

# Pradalex™

## (pradofloxacin injection)

200 mg pradofloxacin/mL injectable solution
Antimicrobial

**CAUTION**

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Federal law prohibits the extra-label use of this drug in food-producing animals.

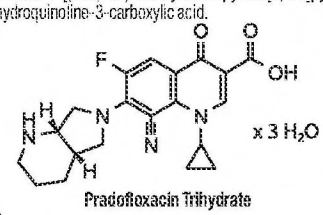
To ensure responsible antimicrobial drug use, use of pradofloxacin should be limited to treatment of bovine respiratory disease (BRD) in cattle and treatment of swine respiratory disease (SRD) in swine only after consideration of other non-fluoroquinolone therapeutic options.

**PRODUCT DESCRIPTION**

Pradalex (pradofloxacin injection) is a sterile, ready-to-use injectable antimicrobial solution that contains pradofloxacin, a broad-spectrum fluoroquinolone antimicrobial agent.

Each mL of Pradalex contains 227 mg pradofloxacin trihydrate; equivalent to 200 mg of pradofloxacin. Excipients are citric acid (antioxidant) 1 mg, gluconolactone (for pH adjustment) 77 mg, and water for injection q.s.

Pradofloxacin is a fluoroquinolone antimicrobial and belongs to the class of quinoline carboxylic acid derivatives. Its chemical name is 8-cyano-1-cyclopropyl-6-fluoro-7-[(4aS,7aS)-octahydro-6H-pyrrolo[3,4-b]pyridin-6-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.




**Pradofloxacin Trihydrate**

**INDICATIONS**

**Cattle:** Pradalex is indicated for the treatment of BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* in cattle intended for slaughter (beef calves 2 months of age and older, growing beef steers, growing beef heifers, and beef bulls intended for slaughter), and in cattle intended for breeding less than 1 year of age (replacement beef and dairy heifers less than 1 year of age and beef and dairy bulls less than 1 year of age). Not for use in cattle intended for breeding 1 year of age and older (replacement beef and dairy heifers 1 year of age and older, beef and dairy bulls 1 year of age and older, and beef and dairy cows), beef calves less than 2 months of age, dairy calves, and veal calves.

**Swine:** Pradalex is indicated for the treatment of SRD associated with *Bordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida, Streptococcus suis,* and *Mycoplasma hyopneumoniae* in weaned swine intended for slaughter (nursery, growing, and finishing swine, boars intended for slaughter, barrows, gilts intended for slaughter, and sows intended for slaughter).

Not for use in swine intended for breeding (boars intended for breeding, replacement gilts, and sows intended for breeding) and in nursing piglets.

**DOSAGE AND ADMINISTRATION**

**Cattle:** Administer once as a subcutaneous injection at a dosage of 10 mg/kg (2.3 mL/100 lb) body weight. Do not inject more than 15 mL per subcutaneous injection site.

**Table 1.** Pradalex Dose Guide for Cattle (2.3 mL/100 lbs)

| Weight (lb) | Dose Volume (mL) |
|---|---|
| 100 | 2.3 |
| 200 | 4.6 |
| 300 | 6.9 |
| 400 | 9.2 |
| 500 | 11.5 |
| 600 | 13.8 |
| 700 | 16.1 |
| 800 | 18.4 |
| 900 | 20.7 |

**Swine:** Administer once as an intramuscular injection in the neck at a dosage of 7.5 mg/kg (1.7 mL/100 lb) body weight. Do not inject more than 5 mL per intramuscular injection site.

**Table 2.** Pradalex Dose Guide for Swine (1.7 mL/100 lbs)

| Weight (lb) | Dose Volume (mL) |
|---|---|
| 15 | 0.3 |
| 30 | 0.5 |
| 50 | 0.9 |
| 100 | 1.7 |
| 150 | 2.6 |
| 200 | 3.4 |
| 250 | 4.3 |

**Dilution of Pradalex:** Pradalex may be diluted with sterile water, sterile saline (0.9%), or 5% dextrose (D5W) prior to injection. The diluted product should be used within 24 hours. Store diluted solution in amber glass bottles between 25-40°C (77-104°F).

**Table 3.** Dilution Guide for Swine*

| Swine Weight | mL of Pradalex | mL of diluent** | Number of doses |
|---|---|---|---|
| 5 lb | 8.5 mL | 91.5 mL | 100 |
| 10 lb | 17 mL | 83 mL | 100 |
| 15 lb | 25.6 mL | 74.4 mL | 100 |
| 20 lb | 34.1 mL | 65.9 mL | 100 |
| 25 lb | 42.6 mL | 57.4 mL | 100 |
| 30 lb | 51.1 mL | 48.9 mL | 100 |
| 35 lb | 59.7 mL | 40.3 mL | 100 |
| 40 lb | 68.2 mL | 31.8 mL | 100 |
| 45 lb | 76.7 mL | 23.3 mL | 100 |
| 50 lb | 85.2 mL | 14.8 mL | 100 |

*For 1 mL dose volume from diluted solution
**Pradalex can be diluted with sterile water, sterile saline (0.9%), or 5% dextrose (D5W) for injection

Use bottle within 6 months of first puncture. When administering from the 250 mL bottle, puncture a maximum of 120 times. If more than 120 punctures are anticipated, the use of multi-dosing equipment is recommended. When using a draw-off spike or needle with bore diameter larger than 16-gauge, discard any product remaining in the vial immediately after use.

**WITHDRAWAL PERIODS and RESIDUE WARNINGS**

Cattle intended for human consumption must not be slaughtered within 4 days of treatment. Swine intended for human consumption must not be slaughtered within 2 days of treatment. Not for use in female dairy cattle 1 year of age and older, including dry dairy cows; use in these cattle may cause drug residues in milk and/or in calves born to these cows. Not for use in beef calves less than 2 months of age, dairy calves, and veal calves; a withdrawal period has not been established for this product in pre-ruminating calves.

**USER SAFETY WARNINGS**

Not for use in humans. Keep out of reach of children. Avoid contact with eyes and skin. In case of ocular contact, immediately remove contact lenses and flush eyes with copious amounts of water for 15 minutes. In case of dermal contact, wash skin with soap and water for at least 20 seconds. Consult a physician if irritation persists following ocular or dermal exposures, or in case of accidental ingestion. Individuals with a history of hypersensitivity to quinolones should avoid this product. In humans, there is a risk of user photosensitization within a few hours after excessive exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. Do not eat, drink or smoke while handling this product. To obtain a copy of the Safety Data Sheet, contact Elanco at 1-800-428-4441.

**ANIMAL SAFETY WARNINGS**

Not for use in animals intended for breeding because the effects of Pradalex on bovine and swine reproductive performance, pregnancy, and lactation have not been determined. Not for use in pre-ruminating calves or nursing piglets because safety and effectiveness has not been demonstrated. Swelling and inflammation may be seen at the injection site after administration. These local tissue reactions may persist beyond the slaughter withdrawal period and may result in trim loss of edible tissue at slaughter.

Quinolones should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation that may lead to convulsive seizures. Quinolones have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species. See Target Animal Safety section for additional information.

**ADVERSE REACTIONS**

Mild to moderate inflammatory changes of the injection site may be seen in cattle and swine treated with Pradalex.

**CONTACT INFORMATION**

To report suspected adverse drug experiences, for technical assistance or to obtain a copy of the Safety Data Sheet, contact Elanco at 1-800-428-4441. For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

**CLINICAL PHARMACOLOGY**

**Mechanism of Action**

Pradofloxacin is a synthetic fluoroquinolone antibacterial drug. Pradofloxacin acts via inhibition of DNA gyrase and topoisomerase IV enzymes in bacteria to inhibit DNA and RNA synthesis. It is bactericidal with a broad spectrum of activity. As a class, fluoroquinolones are considered concentration dependent antimicrobials. Pradofloxacin induces long post-antibiotic effects (PAE) and extended post-antibiotic sub-MIC effects (PA SME), both in aerobic and anaerobic bacteria.

**Pharmacokinetics**

**Cattle:** The pharmacokinetic parameters of pradofloxacin in Table 4 were determined from two studies following subcutaneous administration of pradofloxacin in 4- to-5-month-old weaned calves weighing 158 to 319 kg.

PA6X0276X

Elanco™ Pradalex™ (pradofloxacin injection)

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Pradofloxacin exposure (Cmax and AUC) was dose proportional over a 10 to 50 mg/kg dose range with no accumulation when administered once every 4 days over 8 days.

Pradofloxacin was excreted in both the urine and the feces, largely unchanged, with the majority of the administered dose being excreted in the first 24 hours post-dosing.

**Swine:** The pharmacokinetic parameters of pradofloxacin in Table 4 were determined following intramuscular administration of pradofloxacin in 18-day-old weaned pigs weighing 5.5 to 7.9 kg. Pradofloxacin exposure ($C_{max}$ and AUC) was dose proportional over a 7.5 to 37.5 mg/kg dose range with no accumulation when administered once every 2 days over 4 days.

Pradofloxacin was excreted in both the urine and the feces, largely unchanged, with approximately one-third of the administered dose being excreted in the first 24 hours post-dosing.

**Table 4.** Arithmetic mean (± standard deviation) plasma pradofloxacin pharmacokinetic parameters following the first of three administrations of Pradalex (pradofloxacin injection).

| Pharmacokinetic Parameter | Weaned calves (N=12) 10 mg/kg BW SC | Weaned pigs (N = 8) 7.5 mg/kg BW IM |
|---|---|---|
| $C_{max}$ (µg/mL) | 1.9 ± 0.4 | 2.5 ± 1.9 |
| $T_{max}$ (hours)[a] | 1 (1 to 2) | 0.75 (0.5 to 2) |
| $AUC_{last}$ (hr*µg/mL) | 10.5 ± 1.2 | 26.2 ± 3.7 |
| $t_{1/2}$ (hours) | 2.8 ± 0.4[b] | 8.5 ± 2.6 |

[a] Reported as: Median (range)
[b] N=11 due to inability to calculate half-life in 1 animal
$C_{max}$ = maximum concentration
$T_{max}$ = time to maximum concentration
$AUC_{last}$ = area under the curve from the time of dosing to the time of the last measurable concentration
$t_{1/2}$ = half-life

## MICROBIOLOGY

**Cattle:** The minimal inhibitory concentrations (MICs) of pradofloxacin were determined for isolates of *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni,* and *Mycoplasma bovis* which were obtained from cattle enrolled in the 2015 BRD field study conducted in the U.S. MIC determinations were completed using Clinical and Laboratory Standards Institute (CLSI) standard methods except for *M. bovis*. The methods and quality control performance standards for *M. bovis* were validated with a multi-center laboratory study. The results are shown below in Table 5.

**Table 5.** Pradofloxacin MIC values* of BRD pathogens isolated from the 2015 field study.

| BRD Pathogens | No. of Isolates | MIC50** (µg/mL) | MIC90** (µg/mL) | MIC range (µg/mL) |
|---|---|---|---|---|
| *M. haemolytica* | 365 | 0.008 | 2 | 0.001 to 2 |
| *P. multocida* | 248 | 0.008 | 0.015 | 0.001 to 0.12 |
| *H. somni* | 106 | 0.015 | 0.015 | 0.015 to 0.25 |
| *M. bovis* | 159 | 0.12 | 0.5 | 0.002 to 1 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

**Swine:** The MICs of pradofloxacin were determined for isolates of *Bordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida* and *Streptococcus suis* which were obtained from swine enrolled in the 2017 SRD field study conducted in the U.S. MIC determinations were completed using CLSI standard methods except for *G. parasuis*. The methods for *G. parasuis* were validated with a multi-center laboratory study. The results are shown below in Table 6.

**Table 6.** Pradofloxacin MIC values* of SRD pathogens isolated from the 2017 field study.

| SRD Pathogens | No. of Isolates | MIC50** (µg/mL) | MIC90** (µg/mL) | MIC range (µg/mL) |
|---|---|---|---|---|
| *B. bronchiseptica* | 111 | 0.12 | 0.12 | 0.12 to 0.25 |
| *G. parasuis* | 93 | 0.001 | 0.004 | 0.00025 to 0.008 |
| *P. multocida* | 99 | 0.004 | 0.008 | 0.004 to 0.008 |
| *S. suis* | 212 | 0.06 | 0.25 | 0.015 to 4 |

* The correlation between *in vitro* susceptibility data and clinical effectiveness is unknown.
** The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.

## EFFECTIVENESS

**Cattle:** The effectiveness of Pradalex for the treatment of BRD associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* was demonstrated in a multi-site natural infection field study conducted in the U.S. A total of 630 commercial, mixed-breed male and female calves with clinical BRD were enrolled. Calves were administered a single subcutaneous dose of either Pradalex at 10 mg/kg body weight or an equivalent volume of sterile saline. Calves were evaluated for clinical success on Day 10. The success rate of Pradalex-treated calves (49.7%) was statistically significantly different (p = 0.0089) and numerically greater than that of saline-treated calves (25.6%) (based on back-transformed least squares means). No adverse events associated with Pradalex administration were reported in the study.

**Swine:** The effectiveness of Pradalex for the treatment of SRD associated with *Bordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida, Streptococcus suis,* and *Mycoplasma hyopneumoniae* was demonstrated in a multi-site, natural infection field study conducted in the U.S. A total of 1,200 castrated male and female growing pigs with clinical SRD were enrolled. At enrollment, pigs were administered a single intramuscular dose of either Pradalex at 7.5 mg/kg body weight, or an equivalent volume of sterile saline. Pigs were evaluated for clinical success on Day 7. The success rate of Pradalex-treated pigs (45.2%) was statistically significantly different (p=0.0274) and numerically greater than that of the saline-treated pigs (34.2%) (based on least squares means). No adverse events associated with Pradalex administration were reported in the study.

A total of 72 castrated male and female growing pigs were enrolled in an *M. hyopneumoniae*-induced challenge model study. Pigs were inoculated with a field strain of *M. hyopneumoniae* once daily for three consecutive days. Three days after the final inoculation, pigs were administered a single intramuscular dose of either Pradalex at 7.5 mg/kg body weight, or an equivalent volume of sterile saline. Pigs were euthanized and necropsied on Day 10. There was a significant difference (p=0.0002) in the mean total lung lesion score in favor of Pradalex-treated pigs (11.7%) compared to the saline-treated pigs (33.1%).

## TARGET ANIMAL SAFETY

**Cattle:** Pradalex was evaluated in a margin of safety study with 32 healthy, weaned calves. Calves were randomized to four treatment groups: 0X (saline control), 1X (10 mg pradofloxacin/kg), 3X (30 mg pradofloxacin/kg) and 5X (50 mg pradofloxacin/kg). Calves were administered subcutaneous doses on Days 0, 4, and 8. All calves remained clinically normal throughout the in-life study and survived until scheduled necropsy on Day 9. Injection site swelling was noted in the 1X and 5X groups. Neutrophil counts, monocyte counts, and creatine kinase levels were generally higher in the treated groups, and this was attributed to inflammation and tissue damage at the injection sites. At necropsy, injection site lesions consisting of discoloration and edema, with microscopically visible hemorrhage, inflammation, and necrosis were reported in most treated animals. No signs of fluoroquinolone-induced arthropathy were reported. No other clinically significant adverse effects related to Pradalex were reported.

Pradalex was also evaluated in a margin of safety study focusing on pathologic changes to the testes and epididymides in 16 healthy, weaned bull calves. Calves were randomized to four treatment groups: 0X (saline control), 1X (10 mg pradofloxacin/kg), 3X (30 mg pradofloxacin/kg) and 5X (50 mg pradofloxacin/kg). Calves were administered subcutaneous doses on Days 0, 4, and 8. All calves remained clinically normal throughout the study and survived until scheduled castration on Day 9. Injection site swelling was noted in the 1X, 3X, and 5X groups. In the 1X group, 3 of 4 calves developed mild to moderate subcutaneous swellings, one resolved by 6 hours post-treatment and two were not resolved by the end of the study. No abnormal macroscopic or microscopic pathology in the testes or epididymides was reported.

**Swine:** Pradalex was evaluated in a margin of safety study with 32 healthy, weaned, crossbred pigs. Pigs were randomized to four treatment groups: 0X (saline control), 1X (7.5 mg pradofloxacin/kg), 3X (22.5 mg pradofloxacin/kg) and 5X (37.3mg pradofloxacin/kg). Pigs were administered intramuscular doses on Days 0, 2, and 4. All pigs remained clinically normal throughout the in-life study and all pigs survived until scheduled necropsy on Day 11. Aspartate aminotransferase (AST) and creatine phosphokinase (CK) showed elevations and statistically significant treatment by day interactions in Pradalex-treated pigs. These were attributed to inflammation and tissue damage at the injection sites and the values returned to normal by Day 10. There were no other clinically relevant effects on the remaining clinical pathology results. At necropsy, the only macroscopic and microscopic lesions attributable to Pradalex were related to tissue injury at the intramuscular injection sites. No signs of fluoroquinolone-induced arthropathy were reported. No other clinically significant adverse effects related to Pradalex were reported.

## STORAGE CONDITIONS

Protect from direct sunlight. Do not refrigerate or freeze. Store at 25°C (77°F), excursions permitted up to 40°C (104°F) and down to -20°C (-4°F).

See in-use instructions provided in the Dosage and Administration section.

## HOW SUPPLIED

200 mg/mL 250 mL bottles
200 mg/mL 100 mL bottles

Pradalex is protected by one or more U.S. patents; see patent information at http://www.elancopatents.com

Approved by FDA under NADA # 141-550



Product of Germany

Manufactured by TriRx Pharmaceutical Services, Shawnee Mission, Kansas 66216 U.S.

Revision January 2024

TAKE TIME

OBSERVE LABEL DIRECTIONS

Elanco™

PA6I0276X

**PRODUCT INFO**

| | | | |
|---|---|---|---|
| BLUE #: | 600276Mmm | Product Name: | Pradaxa |
| Item Code: | PA600276X | Component: | Package Inserts and Leaflets |
| Product Code: | N/A | Pack Size: | Multi |
| Previous Item Code | N/A | | |

**ARTWORK INFO**

| | | | |
|---|---|---|---|
| Template: | 7.875 x 9.8125 in | Packaging Specific: | N/A |
| Barcodes/Type: | Code 128/ B1SS | Add. Info: | N/A |
| | | Minimum Core Data Point Size: | 8pt |
| GTIN: | GTIN Not Required | Proof # P2a | By/Date CY 05-Jan-2024 |

NON PRINTING BLACK

BLANK0 ARTWORK LEGEND v16

# Exhibit C

U.S. FOOD & DRUG ADMINISTRATION

N-141550-A-0000-OT

Elanco US Inc
Attention: Jennifer T. Schofield, DVM, CPH
Advisor, Regulatory Innovation
2500 Innovation Way
Greenfield, IN 46140-9163

Re: Original approval

Dear Dr. Schofield:

We approve the original new animal drug application (NADA) for Pradalex™ you submitted, under section 512(c)(1) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act). We received the application on February 15, 2024. Pradalex™ (pradofloxacin injection) injectable solution is approved for the following indications:

Cattle: Pradalex™ is indicated for the treatment of bovine respiratory disease (BRD) associated with *Mannheimia haemolytica, Pasteurella multocida, Histophilus somni* and *Mycoplasma bovis* in cattle intended for slaughter (beef calves 2 months of age and older, growing beef steers, growing beef heifers, and beef bulls intended for slaughter), and in cattle intended for breeding less than 1 year of age (replacement beef and dairy heifers less than 1 year of age and beef and dairy bulls less than 1 year of age). Not for use in cattle intended for breeding 1 year of age and older (replacement beef and dairy heifers 1 year of age and older, beef and dairy bulls 1 year of age and older, and beef and dairy cows), beef calves less than 2 months of age, dairy calves, and veal calves.

Swine: Pradalex™ is indicated for the treatment of swine respiratory disease (SRD) associated with *Bordetella bronchiseptica, Glaesserella (Haemophilus) parasuis, Pasteurella multocida, Streptococcus suis,* and *Mycoplasma hyopneumoniae* in weaned swine intended for slaughter (nursery, growing, and finishing swine, boars intended for slaughter, barrows, gilts intended for slaughter, and sows intended for slaughter). Not for use in swine intended for breeding (boars intended for breeding, replacement gilts, and sows intended for breeding) and in nursing piglets.

The expiration dating for this new animal drug is 36 months. We forwarded a notice of this approval for publication in the FEDERAL REGISTER. You must notify us of any change to the conditions established in this approval according to 21 CFR 514.8. Any change to the conditions of the approval may require the submission of a supplemental application.

Pradalex™, as approved in this letter, qualifies for THREE years of marketing exclusivity beginning as of the date of this letter. This drug qualifies for exclusivity under section 512(c)(2)(F)(ii) of the FD&C Act because you submitted an original NADA that contains new studies that demonstrate the safety and effectiveness of Pradalex™.

Your final printed labeling must be identical to the approved labeling received on February 15, 2024 (A-0000, 12 x 100 mL shipper and 12 x 250 mL shipper). Your labeling was considered facsimile because information regarding the size of the label was not included. Please submit a single copy of each component of the final printed labeling before distributing and marketing your new animal drug. The labeling should be submitted via eSubmitter in Portable Document Format (.pdf) files, which are an exact electronic representation of the final labeling. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

Your final printed labeling received on February 15, 2024 (A-0000, package insert, 100 mL vial and carton, 250 mL vial and carton), is acceptable. It is not necessary to resubmit this labeling. Any changes to this approved labeling will require a supplemental application (see 21 CFR 514.8(c)).

Under current good manufacturing practice (cGMP) regulations (21 CFR parts 211 and 226), you are required to validate your manufacturing processes. This validation provides assurance that the manufacturing processes will reliably meet predetermined specifications. This validation is demonstrated by documenting that the manufacturing processes are adequate to preserve the identity, strength, quality, and purity of the new animal drug. If your validation information was not available or was found deficient at the time of the pre-approval inspection, you should contact FDA after you complete manufacturing validation and before you ship the product. A product that does not conform to cGMP is adulterated under section 501(a) of the FD&C Act.

If you submit correspondence relating to this letter, your correspondence should reference the date and the principal submission identified in this letter. If you have any questions or comments, please contact Dr. John Mussman, Leader, Antimicrobial Drugs Team, at 240-402-0589 or at john.mussman@fda.hhs.gov.

If you have questions or need assistance with the drug development process or project updates, contact your project manager. If you do not know who your project manager is, send an email to CVM.ONADE.PM@fda.hhs.gov.

Sincerely,

*(see appended electronic signature page)*
Tracey H. Forfa, J.D., M.Div.
Director
Center for Veterinary Medicine

Enclosure:
Freedom of Information Summary

# Electronic Signature Addendum for Submission ID

N-141550-A-0000-OT

| Signing Authority (Role) | Letter Date |
| --- | --- |
| William Flynn (Center Director) - Acting | 4/9/2024 |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

# Exhibit D

# Veraflox™

(pradofloxacin)

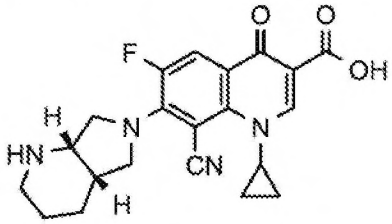
**Oral Suspension for Cats**
**25 mg/mL**
**Do not use in dogs.**
**Federal law prohibits the extralabel use of this drug in food-producing animals.**

## CAUTION

Federal law restricts this drug to use by or on the order of a licensed veterinarian.

## DESCRIPTION

Pradofloxacin is a fluoroquinolone antibiotic and belongs to the class of quinoline carboxylic acid derivatives. Its chemical name is: 7-[(4aS) octahydro-6H-pyrrolo [3, 4-b] pyridine-6yl]-8-cyano-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinoline carboxylic acid. Each mL of VERAFLOX Oral Suspension provides 25 mg of pradofloxacin.



## INDICATION

VERAFLOX is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and *Staphylococcus pseudintermedius*.

## DOSAGE AND ADMINISTRATION

Shake well before use. To ensure a correct dosage, body weight should be determined as accurately as possible. The dose of VERAFLOX is 7.5 mg/kg (3.4 mg/lb) body weight once daily for 7 consecutive days. Use the syringe provided to ensure accuracy of dosing to the nearest 0.1 mL. Rinse syringe between doses.

A sample of the lesion should be obtained for culture and susceptibility testing prior to beginning antibacterial therapy. Once results become available, continue with appropriate therapy. If acceptable response to treatment is not observed, or if no improvement is seen within 3 to 4 days, then the diagnosis should be re-evaluated and appropriate alternative therapy considered.

## CONTRAINDICATIONS

**DO NOT USE IN DOGS. Pradofloxacin has been shown to cause bone marrow suppression in dogs. Dogs may be particularly sensitive to this effect, potentially resulting in severe thrombocytopenia and neutropenia.**

Quinolone-class drugs have been shown to cause arthropathy in immature animals of most species tested, the dog being particularly sensitive to this side effect.

Pradofloxacin is contraindicated in cats with a known hypersensitivity to quinolones.

## WARNINGS

Human Warnings:

**Not for human use. Keep out of reach of children.**

Individuals with a history of quinolone hypersensitivity should avoid this product. Avoid contact with eyes and skin. In case of ocular contact, immediately flush eyes with copious amounts of water. In case of dermal contact, wash skin with soap and water immediately for at least 20 seconds. Consult a physician if irritation persists following ocular or dermal exposure, or in case of accidental ingestion. In humans, there is a risk of photosensitization within a few hours after exposure to quinolones. If excessive accidental exposure occurs, avoid direct sunlight. Do not eat, drink or smoke while handling this product.

It is recommended that used syringes be kept out of reach of children and disposed of properly.

Animal Warnings:

**For use in cats only.**

**The administration of pradofloxacin for longer than 7 days induced reversible leukocyte, neutrophil, and lymphocyte decreases in healthy, 12-week-old kittens (see Animal Safety section).** If an unexplained drop in leukocyte, neutrophil, and/or lymphocyte counts is noted during pradofloxacin therapy, discontinuation of treatment is recommended.

## PRECAUTIONS

Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

The use of fluoroquinolones in cats has been associated with the development of retinopathy and/or blindness. Such products should be used with caution in cats.

Quinolones have been shown to produce erosions of cartilage of weight-bearing joints and other signs of arthropathy in immature animals of various species.

The safety of pradofloxacin in immune-compromised cats (i.e., cats infected with feline leukemia virus and/or feline immunodeficiency virus) has not been evaluated.

Quinolones should be used with caution in animals with known or suspected central nervous system (CNS) disorders. In such animals, quinolones have, in rare instances, been associated with CNS stimulation that may lead to convulsive seizures. The safety of pradofloxacin in cats younger than 12 weeks of age has not been evaluated.

The safety of pradofloxacin in cats that are used for breeding or that are pregnant and/or lactating has not been evaluated.

DRUG INTERACTIONS: Compounds (e.g., sucralfate, antacids and multivitamins) containing divalent and trivalent cations (e.g., iron, aluminum, calcium, magnesium, and zinc) may substantially interfere with the absorption of quinolones resulting in a decrease in product bioavailability. Therefore, the concomitant oral administration of quinolones with foods, supplements, or other preparations containing these compounds should be avoided.

The dosage of theophylline should be reduced when used concurrently with quinolones. Cimetidine has been shown to interfere with the metabolism of quinolones and should be used with care when used concurrently. Concurrent use of quinolones with oral cyclosporine should be avoided. Concurrent administration of quinolones may increase the action of oral anticoagulants.

## ADVERSE REACTIONS

In a multi-site field study, 282 cats (ages 0.3 to 19 years) were evaluated for safety when given either VERAFLOX at a dose of 7.5 mg/kg (3.4 mg/lb) or placebo (vehicle without active ingredient) at a dose of 0.14 mL/lb (0.3 mL/kg). Each group was treated once daily for 7 consecutive days. Adverse reactions are summarized in Table 1.

**Table 1:** Number of Adverse Reactions Among Cats Treated with Pradofloxacin (N=190) or Vehicle (N=92)*

| Adverse Reactions | Pradofloxacin | Vehicle |
|---|---|---|
| Diarrhea / loose stools | 7 | 2 |
| Leukocytosis with neutrophilia | 4 | 6 |
| Elevated CPK levels | 4 | 4 |
| Sneezing | 4 | 1 |
| Hematuria | 2 | 2 |
| Hypersalivation | 2 | 1 |
| Pruritus | 2 | 0 |
| Inappetence | 1 | 3 |
| Lethargy | 1 | 2 |
| Cardiac murmur | 1 | 1 |
| Reclusive behavior | 1 | 1 |
| Vomiting | 1 | 1 |
| Bacteriuria | 1 | 0 |
| Lymphadenopathy | 1 | 0 |
| Polydipsia | 1 | 0 |
| Upper respiratory infection | 1 | 0 |

* Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

The Safety Data Sheet (SDS) provides additional occupational safety information.

For product questions, to report adverse reactions, or for a copy of the Safety Data Sheet (SDS), call Elanco Product & Veterinary Support at 888-545-5973.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

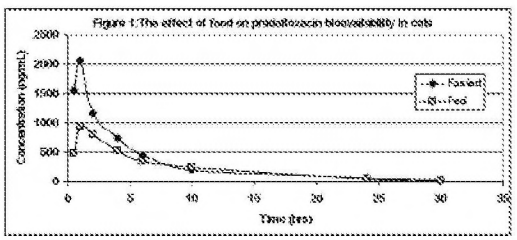
## CLINICAL PHARMACOLOGY

Pharmacokinetics:

Pradofloxacin is rapidly absorbed following oral administration of VERAFLOX to fasted cats, with peak serum concentrations occurring in less than 1 hour. However, food markedly diminishes the serum bioavailability of pradofloxacin; mean peak serum concentrations (Cmax) are reduced 53% and mean exposures (AUC) are decreased by 26%. The relative bioavailability of pradofloxacin, when administered as the 2.5% oral suspension to fed and fasted cats, is provided in Table 2 and Figure 1.

**Table 2.** Mean (1 SD) serum pradofloxacin derived pharmacokinetics parameters in cats (N =12) following a 5mg/kg oral dose of VERAFLOX under fasted and fed conditions.

| | **VERAFLOX 5 mg/kg Dose** | |
|---|---|---|
| **Parameter** | **Fasted** | **Fed** |
| Cmax (ng/mL) | 2116 (549) | 999 (400) |
| Tmax (hr) | 0.8 | 1.4 |
| AUC0-24 | 9111 (1939) | 6745 (1524) |
| Half-Life (hr) | 7.3 (1.7) | 6.4 (1.2) |



Approximately 30% of the total drug concentrations are bound to plasma proteins in drug concentrations ranging from 150 to 1500 ng/mL. Dose proportional increases in drug concentrations are observed when the oral suspension is administered to fasted cats in doses ranging from 2.5 mg/kg to 10 mg/kg. Due to its short elimination half life, there is minimal pradofloxacin accumulation following multiple daily administrations.

**Pharmacodynamics:**
Pharmacodynamics was determined using *in vitro* susceptibility that showed the pathogens *Pasteurella multocida, Staphylococcus pseudintermedius,* and *Streptococcus spp.* had a pradofloxacin $MIC_{90}$ of ≤0.015 to 0.12 ug/mL. The pharmacodynamics metrics ($C_{max}/MIC_{90}$ and $AUC/MIC_{90}$) were estimated using linear regression analysis of free drug steady-state pradofloxacin pharmacokinetics parameters from fasted cats and a pradofloxacin $MIC_{90}$ value of 0.12 ug/mL. The 95% Confidence Intervals about predicted mean $C_{max}/MIC_{90}$ and $AUC/MIC_{90}$ values were 15 to 17 and 70 to 81, respectively. It was concluded that the magnitude of the $C_{max}/MIC_{90}$ and $AUC/MIC_{90}$ values is predictive of product effectiveness when an oral dose of 7.5 mg/kg body weight of the pradofloxacin liquid formulation is administered to fasted cats. In addition, effectiveness was shown for cats dosed at 7.5 mg/kg body weight and fed free choice, or within two hours of dosing, in a field study.

**Microbiology:**
VERAFLOX is bactericidal, with activity against Gram-negative, Gram-positive, and anaerobic bacteria. The mechanism of action is dual targeting through inhibition of DNA gyrase and topoisomerase IV.
The minimum inhibitory concentrations (MICs) for pradofloxacin against *Pasteurella multocida, Streptococcus canis, Staphylococcus aureus, Staphylococcus felis,* and *Staphylococcus pseudintermedius* isolated from skin infections (wounds and abscesses) in cats in a U.S. field study from 2008 to 2009 are listed in Table 3. Only two isolates from two pradofloxacin Treatment Failure cases had elevated pradofloxacin MICs (non-hemolytic *Staph. aureus* - MIC = 2 µg/mL; *E. coli* - MIC = 4 µg/mL).

**Table 3.** Activity of VERAFLOX against Pathogens Isolated from Cats Treated with VERAFLOX in a Clinical Trial in the US in 2008.

| Disease | Pathogen | Clinical Treatment Outcome | Number of Isolates | Sample Collection (Time Relative to Treatment) | $MIC_{50}$ µg/mL | $MIC_{90}$ µg/mL | MIC Range µg/mL |
|---|---|---|---|---|---|---|---|
| Skin Infections | *Pasteurella multocida* | Success | 40 | Pre-Treatment | 0.008 | 0.015 | ≤ 0.004 - 0.03 |
| | | Failure | 11 | Pre-Treatment | 0.008 | 0.008 | ≤ 0.004 - 0.015 |
| | *Streptococcus canis* | Success | 13 | Pre-Treatment | 0.12 | 0.12 | 0.03 - 0.25 |
| | | Failure | 2 | Pre-Treatment | | | 0.06 - 0.12 |
| | *Staphylococcus aureus* | Success | 10 | Pre-Treatment | 0.12 | 0.12 | 0.015 - 0.12 |
| | | Failure | 0 | | | | |
| | *Staphylococcus felis* | Success | 13 | Pre-Treatment | 0.03 | 0.06 | 0.03 - 0.12 |
| | | Failure | 1 | Pre-Treatment | | | 0.06 |
| | *Staphylococcus pseud-intermedius* | Success | 10 | Pre-Treatment | 0.06 | 0.06 | 0.03 - 0.06 |
| | | Failure | 1 | Pre-Treatment | | | 0.03 |

**EFFECTIVENESS**
The clinical effectiveness of VERAFLOX was demonstrated in a multi-site (16 sites) field study. In this masked and randomized study, the effectiveness of VERAFLOX was compared to a placebo control (vehicle without active ingredient). Of the 282 cats enrolled in this study, 190 were treated with VERAFLOX once daily at 7.5 mg/kg (3.4 mg/lb) body weight for 7 consecutive days and 92 were treated with placebo once daily at 0.3 mL/kg body weight for 7 consecutive days. The effectiveness database included 182 cats: 66 placebo (vehicle)-treated cats and 116 VERAFLOX-treated cats. The analysis of this effectiveness database showed that the cure rate was greater in the VERAFLOX group on Day 15, as summarized in Table 4. Study cure rates were determined approximately 15 days after initiation of therapy. The statistical evaluation of the primary effectiveness endpoint (Study Cures) showed that VERAFLOX was different from placebo with 73.4% VERAFLOX study cures versus 38.9% placebo study cures.

**Table 4**: Day 15 Case Classification

| Treatment Group | Percent Cures |
|---|---|
| VERAFLOX N= 116 | 73.4% |
| Placebo N= 66 | 38.9% |
| P-value | 0.0053 |

**ANIMAL SAFETY**
**Target Animal Safety Study:** Safety was evaluated in 32 healthy, 12-week-old kittens administered VERAFLOX once daily at doses of 0, 7.9, 23.7, or 39.5 mg/kg (0, 1, 3, and 5 times the recommended dose) for 21 consecutive days. Additional control (0X) and high-dose (5X) animals were maintained for 45 days after treatment cessation.
There were statistically significant decreases in neutrophils, lymphocytes, and monocytes in the 3X and 5X groups compared to the controls. During the treatment period, one 3X cat and three 5X cats had absolute neutrophil counts below the reference range. Bone marrow cytology results consistent with bone marrow suppression (myeloid hypoplasia) were seen in the 3X neutropenic cat and two of the three 5X neutropenic cats. The 3X cat was neutropenic on the last day of the study prior to scheduled euthanasia, while absolute neutrophil values for the three 5X cats returned to normal either during treatment or after the cessation of treatment.
The most frequent abnormal clinical finding was soft feces. While this was seen in both treated and control groups, it was observed more frequently in the 3X and 5X kittens.

**Ocular Safety Study:** Ocular safety was evaluated in 20 healthy adult cats using pradofloxacin in capsules administered orally, once daily at doses of 30 mg/kg and 50 mg/kg for 23 days. No effects were seen in the following investigated ocular parameters: ophthalmic examinations, ERGs, and optical coherence tomography. Cats receiving 50 mg/kg/day of pradofloxacin showed mild weight loss. Cats receiving 30 and 50 mg/kg/day of pradofloxacin exhibited hypersalivation and vomiting throughout the study. Dose-dependent reductions in white blood cell counts were noted in the pradofloxacin-treated cats. One cat receiving 30 mg/kg/day of pradofloxacin exhibited minimal photoceptor degeneration on light and electron microscopy of a type that differed from enrofloxacin-treated cats (comparator used in this study); the effects of pradofloxacin on these retinal changes is unknown.

**Pilot Toxicity Study:** In an oral toxicity study, 4 cats received pradofloxacin at 50 mg/kg/day for 25 days. All cats exhibited vomiting and hypersalivation. One cat exhibited fluoroquinolone-induced neurologic signs (decreased mobility, staggering, and vocalization) on Day 5 of the study.

**STORAGE CONDITIONS**
Store below 30°C (86°F).
After initial opening, VERAFLOX has demonstrated in-use stability of 60 days.

**HOW SUPPLIED**

| Bottle Size |
|---|
| 15 mL |
| 30 mL |

Approved by FDA under NADA # 141-344
Made in Germany


Manufactured for:
Elanco US Inc.
Greenfield, IN 46140 U.S.A.
Revised: May 2022

# Exhibit E

US007977484B2

(12) **United States Patent**
**Rast et al.**

(10) **Patent No.: US 7,977,484 B2**
(45) **Date of Patent: Jul. 12, 2011**

(54) **CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID**

(75) Inventors: **Hubert Rast**, Leverkusen (DE); **Iris Heep**, Köln (DE); **Alfons Grunenberg**, Dormagen (DE); **Werner Hallenbach**, Monheim (DE); **Jordi Benet-Buchholz**, Altafulla (ES)

(73) Assignee: **Bayer Animal Health GmbH** (DE)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 893 days.

(21) Appl. No.: **11/547,420**

(22) PCT Filed: **Mar. 19, 2005**

(86) PCT No.: **PCT/EP2005/002953**

§ 371 (c)(1),
(2), (4) Date: **Nov. 5, 2007**

(87) PCT Pub. No.: **WO2005/097789**

PCT Pub. Date: **Oct. 20, 2005**

(65) **Prior Publication Data**

US 2008/0125458 A1 May 29, 2008

(30) **Foreign Application Priority Data**

Apr. 1, 2004 (DE) ..... 10 2004 015 981

(51) **Int. Cl.**
***C07D 471/04*** (2006.01)

(52) **U.S. Cl.** ..... **546/113**

(58) **Field of Classification Search** ..... 546/113; 514/300

See application file for complete search history.

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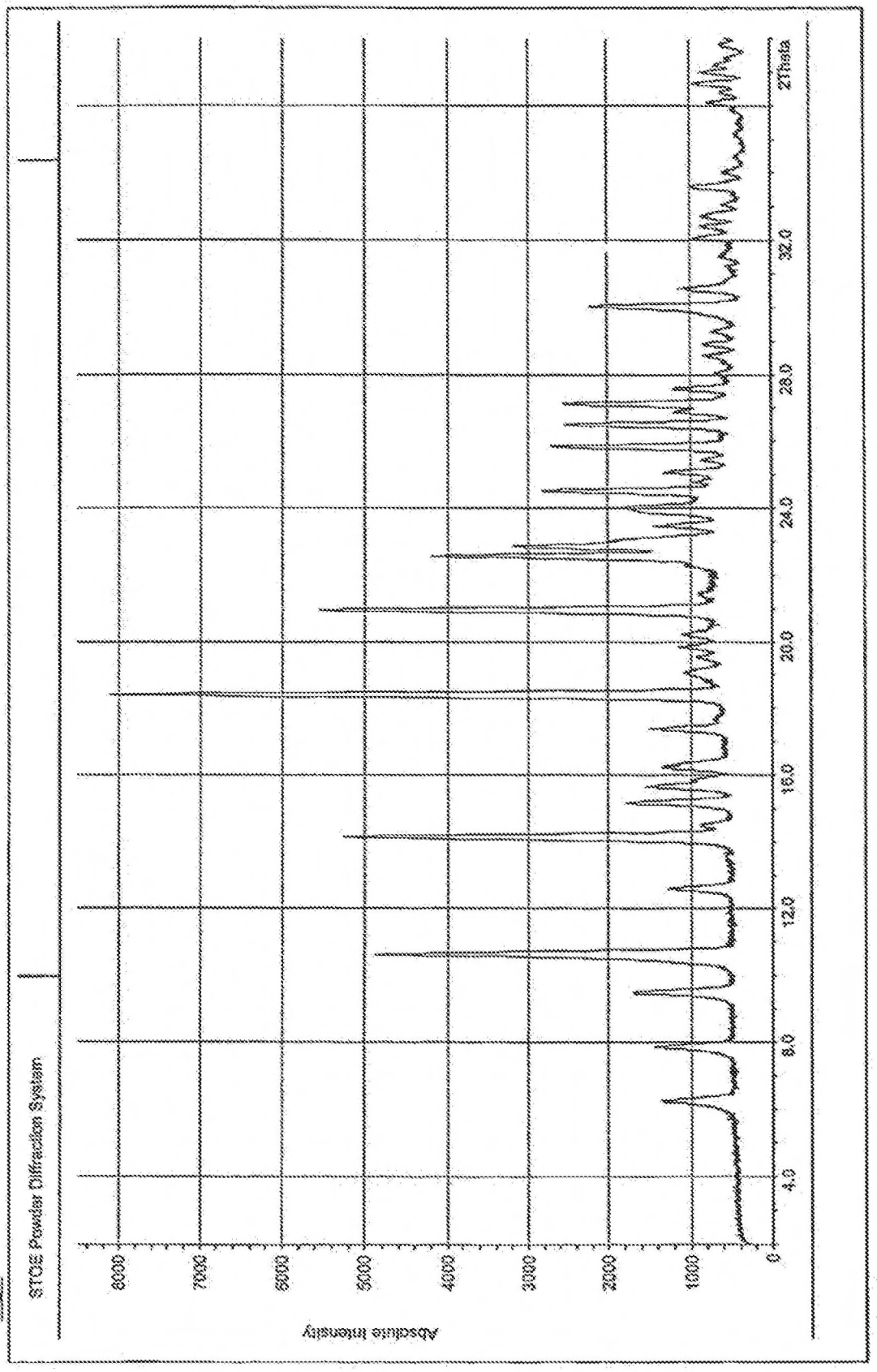
*Primary Examiner* — Patricia Morris

(57) **ABSTRACT**

The present invention relates to the trihydrate of pradofloxacin, to a process for its preparation and to antibacterial compositions comprising them.

**3 Claims, 2 Drawing Sheets**


STOE Powder Diffraction System
Absolute Intensity
8000
7000
6000
5000
4000
3000
2000
1000
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4.0
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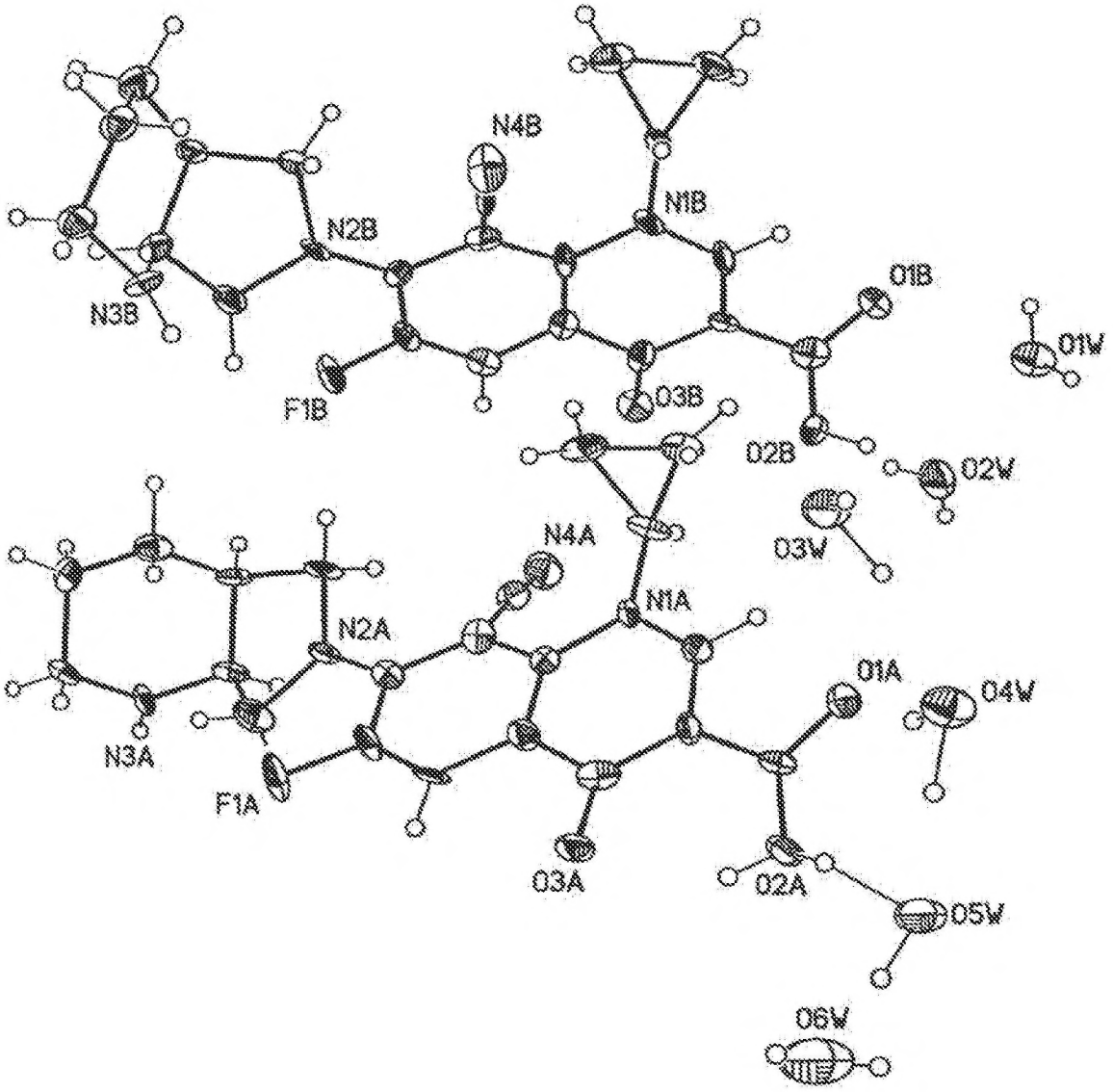
Fig.1

Fig.2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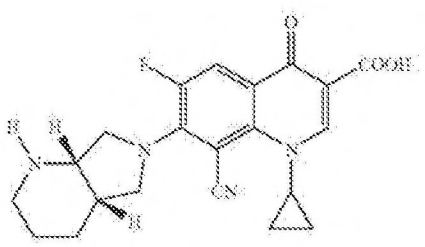
N2A
O1A
O4W
N3A
F1A
O3A
O2A
O5W
O6W

# CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-(1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL)-6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

The present invention relates to the trihydrate of pradofloxacin, to a process for its preparation and to antibacterial compositions comprising it.

The 8-cyano-1-cyclopropyl-7-(1S,6S)-2,8-diazabicyclo[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid of the formula (I) will be referred to hereinbelow by its INN (International Non-proprietary Name) as pradofloxacin.



(I)

Pradofloxacin is known from WO 97/31001. According to this, it is prepared by reacting 7-chloro-8-cyano-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid with (1S,6S)-2,8-diazabicyclo[4.3.0]nonane in a mixture of dimethylformamide and acetonitrile in the presence of an auxiliary base. After admixing with water, pradofloxacin is extracted with dichloromethane from water and isolated by removing the extractant. This gives a powder which does not have any distinct crystal modification. However, it is a prerequisite for the preparation of medicaments that it is possible for an active ingredient which can be present in different crystal modifications to specify unambiguously in which crystal modification it is used to prepare the composition.

The sometimes amorphous powder which is obtained by the above-outlined preparation process is additionally hygroscopic. However, amorphous solids, and especially hygroscopic solids, are difficult to handle in pharmaceutical processing, since they have, for example, low bulk densities and unsatisfactory flow properties. In addition, special working techniques and equipment is required to handle hygroscopic solids in order to obtain reproducible results, for example with regard to the active ingredient content or the stability in the solid formulations produced.

Defined crystal forms of pradofloxacin are already known: modification A (WO 00/31075), modification B (WO 00/31076), modification C (WO 00/52009) and modification D (WO 00/52010), and also the semihydrochloride (WO 00/31077).

Active ingredients for medicaments should be present in forms which are stable even under unfavourable storage conditions, such as elevated temperature and atmospheric moisture. Changes, for example in the crystal structure are undesired, since these often also change important properties, for example the water solubility. In principle, thermodynamically stable crystalline forms of an active ingredient are therefore being sought.

It is an object of the invention to prepare a thermodynamically stable, defined crystal form of pradofloxacin which is suitable for pharmaceutical formulations owing to its properties.



## BRIEF DESCRIPTION OF THE DRAWINGS

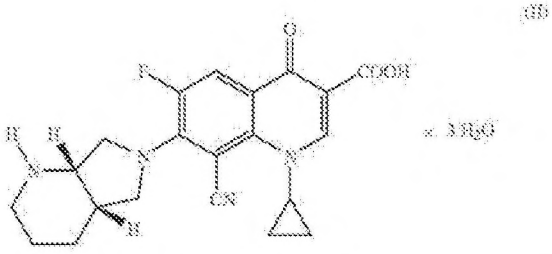
FIG. 1 is the powder X-ray diffractogram of pradofloxacin trihydrate.

FIG. 2 is the structure of pradofloxacin trihydrate in crystal lattice.

## DETAILED DESCRIPTION OF THE INVENTION

Surprisingly, the thermodynamically very stable, hitherto unknown pradofloxacin trihydrate has now been found.

The invention therefore provides pradofloxacin trihydrate; it can be illustrated by the following formula (II):



(II)

Pradofloxacin trihydrate has an X-ray powder diffractogram having the reflections (2 theta), reported in the following Table 1, of high and average intensity (>30% relative intensity).

TABLE 1

| Reflections of average and high intensity ($I_{rel}$ > 30%) of pradofloxacin trihydrate: |
|---|
| 2 θ (2 theta) |
| 10.6256 |
| 14.1386 |
| 18.4032 |
| 20.9422 |
| 22.6604 |
| 22.8420 |
| 24.3165 |
| 25.8426 |
| 26.4972 |
| 26.8759 |
| 27.3221 |

The powder X-ray diffractogram of pradofloxacin trihydrate is reproduced in FIG. 1.

In addition, it was possible to characterize pradofloxacin trihydrate by X-ray structural analysis of a single crystal. Characteristic data are:

| | |
|---|---|
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| Dimensions of the unit cell | a = 12.4299(3) Å α = 90°<br>b = 12.1775(18) Å β = 111.209(6)°<br>c = 15.910(2) Å γ = 90°. |
| Volume | 2130.6(5) Å$^3$ |

The structure in the crystal lattice is shown in FIG. 2.

Pradofloxacin trihydrate can be prepared by the following processes:

A solution of pradofloxacin in a polar aprotic solvent is heated to a temperature of 50° C. or more and then admixed with water which contains seed crystals of pradofloxacin trihydrate.

The solution in the polar aprotic solvent is added preferably at least to the same volume of water, more preferably to 2 to 4 times the volume. It may be advantageous to further heat the resulting mixture to a temperature in the range of 50° C. to the boiling point.

The polar aprotic solvent used should be miscible with water to a sufficient degree; preferred examples are dimethylformamide (DMF), acetonitrile, propionitrile and in particular N-methylpyrrolidone (NMP). It is also possible to use mixtures of these solvents.

Alternatively, pradofloxacin can be heated in water together with a small amount of pradofloxacin trihydrate, preferably to a temperature in the 50 to 100° C. range.

In addition, pradofloxacin trihydrate may also be obtained by reprecipitation via the salts, in which case pradofloxacin trihydrate seed crystals are appropriately added in the course of neutralization.

In the course of reprecipitation, preference is given to dissolving the pradofloxacin in a suitable acid in the presence of water. The solution is then neutralized to pH 7 with a base and the seed crystals are added.

In all processes, the pradofloxacin trihydrate precipitates out as a solid, if necessary after cooling (for example to room temperature).

If required, seed crystals can be prepared by storing a sample of pradofloxacin of the modification B for a prolonged period at an atmospheric moisture content of at least 97%, typically at room temperature.

Pradofloxacin trihydrate is surprisingly stable and is not converted to other crystal forms even in the course of prolonged storage. In addition, pradofloxacin trihydrate does not show any tendency to take up further water from the air. Finally, it can be purified in a simple manner by crystallization. For these reasons, it is outstandingly suitable for preparing medicament formulations, especially those in which the active ingredient is present as a solid. By virtue of its stability, it imparts to these formulations the desired long-lasting storage stability. It is thus possible with pradofloxacin trihydrate to prepare stable formulations of pradofloxacin in a defined and controlled manner.

Pradofloxacin trihydrate is outstandingly effective against pathogenic bacteria in the field of human or veterinary medicine. The action of pradofloxacin trihydrate and thus also its broad field of use corresponds to those of pradofloxacin.

The X-ray powder diffractogram for the characterization of pradofloxacin trihydrate was obtained with a STADI-P transmission diffractometer ($CuK_{\alpha}$ radiation) with location-sensitive detector (PSD2) from Stoe.

The X-ray structural analysis of the single crystal was obtained with a Siemens P4 diffractometer, equipped with a SMART-CCD-1000 two-dimensional detector, a rotating anode (MACScience Co.) with MoK radiation, a graphite monochromator and a Siemens LT2 low temperature apparatus (T=−120° C.).

The examples which follow illustrate the invention without restricting it. The conditions used in the examples which follow are particularly preferred.

## EXAMPLES

### Example A

### Recrystallization from NMP/Water

A.1 120 g of pradofloxacin are heated to 75° C. in 960 ml of peroxide-free N-methylpyrrolidone (NMP). This solution is poured through a fluted filter into 2880 ml of water which have been seeded with pradofloxacin trihydrate. The mixture is allowed to come to room temperature without stirring and left to stand at room temperature for one day. The solid is filtered off with suction, washed twice with 100 ml each time of water and dried under air.

Yield: 115.73 g, 84.9% of theory.

A.2 20 g of pradofloxacin are heated to 75° C. in 90 ml of peroxide-free NMP. Afterwards, 270 ml of water are added and the mixture is heated further to 100° C. The resulting solution is kept at this temperature for another 15 minutes, then cooled somewhat and seeded with pradofloxacin trihydrate. For crystallization, the mixture is left to stand overnight. The solid is filtered off with suction, washed twice with a little water and dried under air.

Yield: 20.44 g, 89.9% of theory.

In all cases, according to the X-ray powder images, pradofloxacin trihydrate was obtained.

### Example B

### Heating in Pure Water

5 g of pradofloxacin and 100 mg of pradofloxacin trihydrate are added to the amount of water specified and heated to the temperature specified for 3 hours.

TABLE 2

Modification conversion by heating in water

| Experiment | Yield | Amount of water | Conditions |
|---|---|---|---|
| B.1 | 91% | 25 ml | 85° C. |
| B.2 | 93% | 50 ml | 85° C. |
| B.3 | 92% | 100 ml | 85° C. |

In all cases, according to X-ray powder images, pradofloxacin trihydrate was obtained.

### Example C

### Reprecipitation Via Salt

TABLE 3

Reprecipitation of pradofloxacin

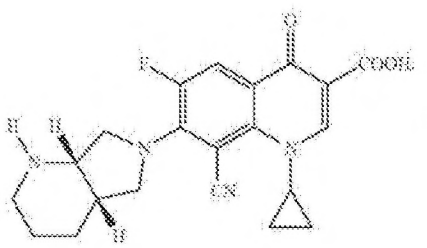
| Experiment | Acid | Amount (mmol) | Yield % | Comment |
|---|---|---|---|---|
| C.1 | Sulphuric acid | 6 | 93.3 | Precipitate at acidic pH |
| C.2 | Acetic acid | 6 | 92 | |
| C.3 | Formic acid | 6 | 81.2 | |
| C.4 | Sulphuric acid | 3 | 94.2 | Precipitate at acidic pH |
| C.5 | Acetic acid | 6 | 89.8 | Precipitated at 60° C. and heat-treated for 2 hours. |

In each case, the specified amount of acid is dissolved in 12 ml of water, 2.4 g (6 mmol) of pradofloxacin are added, and the mixture is stirred for 15 minutes and subsequently neutralized to pH 7.0 with conc. ammonia solution. As soon as the solution becomes cloudy, seed crystals of pradofloxacin trihydrate are added. The mixture is stirred at room temperature overnight, then the solid is filtered off with suction and dried under air.

In all cases, according to X-ray powder images, pradofloxacin trihydrate was obtained.

The invention claimed is:

1. A pradofloxacin trihydrate of formula (II)



(II)

x 3 $H_2O$

2. The pradofloxacin trihydrate of claim 1, having an X-ray powder diffractogram having the reflections

| 2θ (2 theta) |
|---|
| 10.8230 |
| 14.1386 |
| 18.4032 |
| 20.0422 |
| 22.5604 |
| 22.8420 |
| 24.5165 |
| 25.8826 |
| 26.4972 |
| 26.8759 |
| 27.1231 |

of high and average intensity (>30% relative intensity).

3. The pradofloxacin trihydrate of claim 1, wherein the crystal system is monoclinic, the space group is $P2_1$, the dimensions of the unit cell are a=12.4790(18) Å α=90°, b=12.1275(18) Å β=111.009(6)°, c=15.010(2) Å γ=90°, and the volume is 2120.6(5) $Å^3$.

* * * * *

# Exhibit F

# United States Patent and Trademark Office

*Office of the Commissioner for Patents*

## Maintenance Fee Statement

| CURRENT CORRESPONDENCE ADDRESS | CUSTOMER # | ENTITY STATUS | STATEMENT GENERATED |
|---|---|---|---|
| INACTIVE - BAYER HEALTHCARE LLC (AH)<br>1 BAYER DRIVE<br>INDIANOLA, PA 15051 | 71285 | UNDISCOUNTED | 06/03/2024 13:01:01 |

### Invention

NOVEL CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL) -6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

| PATENT # | APPLICATION # | FILING DATE | ISSUE DATE |
|---|---|---|---|
| 7977484 | 11547420 | 11/05/2007 | 07/12/2011 |

### Payment Details

| PAYMENT DATE | DATE POSTED | TRANSACTION ID | ATTORNEY DOCKET # | TOTAL PAYMENT |
|---|---|---|---|---|
| 12/24/2014 | 12/29/2014 | 122914RAMBULKS00009710504623 | BAYER INTELLECTUAL PROP G | $1,600.00 |

| Fee Code | Description | Sale ID | Fee Amount |
|---|---|---|---|
| 1551 | MAINTENANCE FEE DUE AT 3.5 YEARS | 122914RAMBULKS00009710 | $1,600.00 |

*According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.*

# United States Patent and Trademark Office

*Office of the Commissioner for Patents*

## Maintenance Fee Statement

| CURRENT CORRESPONDENCE ADDRESS | CUSTOMER # | ENTITY STATUS | STATEMENT GENERATED |
|---|---|---|---|
| INACTIVE - BAYER HEALTHCARE LLC (AH)<br>1 BAYER DRIVE<br>INDIANOLA, PA 15051 | 71285 | UNDISCOUNTED | 06/03/2024 13:01:08 |

### Invention

NOVEL CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL) -6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

| PATENT # | APPLICATION # | FILING DATE | ISSUE DATE |
|---|---|---|---|
| 7977484 | 11547420 | 11/05/2007 | 07/12/2011 |

### Payment Details

| PAYMENT DATE | DATE POSTED | TRANSACTION ID | ATTORNEY DOCKET # | TOTAL PAYMENT |
|---|---|---|---|---|
| 12/28/2018 | 12/28/2018 | 122818INTMTFEE00007318504623 | | $3,600.00 |

| Fee Code | Description | Sale ID | Fee Amount |
|---|---|---|---|
| 1552 | MAINTENANCE FEE DUE AT 7.5 YEARS | 122818INTMTFEE00007318 | $3,600.00 |

*According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.*

# United States Patent and Trademark Office

*Office of the Commissioner for Patents*

## Maintenance Fee Statement

| CURRENT CORRESPONDENCE ADDRESS | CUSTOMER # | ENTITY STATUS | STATEMENT GENERATED |
|---|---|---|---|
| INACTIVE - BAYER HEALTHCARE LLC (AH)<br>1 BAYER DRIVE<br>INDIANOLA, PA 15051 | 71285 | UNDISCOUNTED | 06/03/2024 13:01:15 |

### Invention

NOVEL CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL) -6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

| PATENT # | APPLICATION # | FILING DATE | ISSUE DATE |
|---|---|---|---|
| 7977484 | 11547420 | 11/05/2007 | 07/12/2011 |

### Payment Details

| PAYMENT DATE | DATE POSTED | TRANSACTION ID | ATTORNEY DOCKET # | TOTAL PAYMENT |
|---|---|---|---|---|
| 12/14/2022 | 12/14/2022 | E2022BD809410965 | 10418586 | $7,700.00 |

| Fee Code | Description | Ref ID | Fee Amount |
|---|---|---|---|
| 1553 | MAINTENANCE FEE DUE AT 11.5 YEARS | E2022BD809410965 | $7,700.00 |

*According to the records of the United States Patent and Trademark Office (USPTO), the maintenance fee and any necessary surcharge have been timely paid for the patent listed above. The payment shown above is subject to actual collection. If the payment is refused or charged back by a financial institution, the payment will be void and the maintenance fee and any necessary surcharge unpaid.*

# United States Patent and Trademark Office

*Office of the Commissioner for Patents*

## NOVEL CRYSTALLINE FORM OF CYANO-1-CYCLOPROPYL-7-1S,6S-2,8-DIAZABICYCLO[4.3.0]NONAN-8-YL) -6-FLUORO-1,4-DIHYDRO-4-OXO-3-QUINOLINE CARBOXYLIC ACID

| PATENT # | APPLICATION # | FILING DATE | ISSUE DATE |
|---|---|---|---|
| 7977484 | 11547420 | 11/05/2007 | 07/12/2011 |

## Payment Window Status

No maintenance fees are due.

| WINDOW | STATUS | FEES |
|---|---|---|
| 11.5 Year | Closed | Paid |

| Window | First Day to Pay | Surcharge Starts | Last Day to Pay | Status | Fees |
|---|---|---|---|---|---|
| 3.5 Year | 07/12/2014 | 01/13/2015 | 07/13/2015 | Closed | Paid |
| 7.5 Year | 07/12/2018 | 01/16/2019 | 07/12/2019 | Closed | Paid |
| 11.5 Year | 07/12/2022 | 01/13/2023 | 07/12/2023 | Closed | Paid |

## Patent Holder Information

| | |
|---|---|
| **Customer #** | 71285 |
| **Entity Status** | UNDISCOUNTED |
| **Phone Number** | 4127672400 |
| **Address** | INACTIVE - BAYER HEALTHCARE LLC (AH)<br>1 Bayer Drive<br>Indianola, PA 15051<br>UNITED STATES |

# Exhibit G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date: 06/18/2013

To: mary.hagler@bayer.com
Subject: FDA CVM EDSR – User Submission Notification

The Center for Veterinary Medicine, Food and Drug Administration acknowledges the receipt of your eSubmitter submission to the FDA CVM Electronic Submission System. The following information documents the state of your submission. If you have any questions, please submit an email detailing your questions to cvmesubmitter@fda.hhs.gov.

Memo:
Your submission has been accepted and has been forwarded for review. A document ID has been issued.

| | | | |
|---|---|---|---|
| CVM Received Date: | 06/18/2013 | | |
| Transmission Identifier: | ci1371587865399.189591@llnap31_te | | |
| Submission Identifier: | I-012380-A-0000-OT | Review Division: | HFV-130 |
| Firm Name: | Bayer HealthCare LLC Animal Health Division | | |
| Established Drug Name(s): | | | |
| Submitted Document Type: | INVESTIGATIONAL NEW ANIMAL DRUG | | |
| Submission Type: | INITIAL SUBMISSION | | |
| Correspondence Date: | 06/18/2013 | CVM Due Date: | 09/26/2013 |
| Parent Submission: | | Reference Submission: | |

Notes:

Digital Signature:
Certification signature by CVM ESS, Validity Unknown
Digitally signed by CVM ESS
Date: 2013.06.18 16:42:33 EDT
Reason: I am the author of this document

| Department of Health and Human Services<br>Food and Drug Administration<br>Center for Veterinary Medicine | **Electronic Submission Administrative Cover Sheet** | 06/18/2013 |
|---|---|---|

| Correspondence Date | Document Type | Document # | Submission Type | Submission Class | |
|---|---|---|---|---|---|
| 06/18/2013 | I | | A | OT | HFV- 130 |

## Purpose of Submission

Establish INAD File

## Firm Information

Firm Name: Bayer HealthCare LLC Animal Health Division
Address - Line 1: 12809 Shawnee Mission Pkwy
Address - Line 2:
City: Shawnee
State, Province, or Territory: KS
Country: US
Postal Code or Zip Code: 66216
Telephone Number: (913) 268-2000
DUNS Number: 152266193

## Responsible Official Information

Title (Mr., Ms., Dr.): Ms.
Occupation Title: Regulatory Affairs Manager
First/Given Name: Mary
Middle Name: K.
Last Name: Hagler
Email Address: mary.hagler@bayer.com
Firm Name: Bayer HealthCare LLC Animal Health Division
Address - Line 1: 12809 Shawnee Mission Pkwy
Address - Line 2:
City: Shawnee
State, Province, or Territory: KS
Country: US
Postal Code or Zip Code: 66216
Telephone Number: (913) 268-2553
DUNS Number: 152266193

## Submitter Information

Title (Mr., Ms., Dr.): Ms.
Occupation Title: Regulatory Affairs Manager
First/Given Name: Mary
Middle Name: K.
Last Name: Hagler
Email Address: mary.hagler@bayer.com
Firm Name: Bayer HealthCare LLC Animal Health Division
Address - Line 1: 12809 Shawnee Mission Pkwy
Address - Line 2:
City: Shawnee
State, Province, or Territory: KS
Country: US
Postal Code or Zip Code: 66216
Telephone Number: (913) 268-2553
DUNS Number: 152266193

I certify that:

- I have personally reviewed this submission (or received assurances from qualified personnel) and determined that this submission and all supporting data are true, accurate, and complete to the best of my knowledge and belief,
- For any information submitted by reference in this submission, I/we have submitted to FDA documentation granting the right of reference and I/we have confirmed to the best of our ability that the information contained in the referenced file is true, accurate, and complete,
- No services of any person debarred under section 306(a) of the Federal Food, Drug, and Cosmetic Act have been used in any capacity related to this submission, and
- I am aware there are significant penalties for submitting false information, including the possibility of fine and imprisonment for knowing and willful violations (18 U.S.C. § 1001).

Further, I agree:

- To comply with all applicable statutes and regulations governing the investigational use and approval of new animal drugs.

Responsible Official

Mary Hagler
Digitally Signed On: 06/18/2013, 08:32:47 PM

# Submission Report

## Section: CVM ONADE SUBMISSIONS

### 1.0 Document Information

*Department of Health and Human Services*
*Food and Drug Administration*

**CENTER FOR VETERINARY MEDICINE**

**Welcome to the Office of New Animal Drug Evaluation eSubmitter Program**

This electronic submission tool automates the submission process for all regulatory submissions destined for CVM's Office of New Animal Drug Evaluation (ONADE). The software contains all of the templates necessary to build any submission reviewed by ONADE. The user will select a submission type and be presented with a question-based approach to guide them through the submission creation process. The questions asked throughout the process are founded on the Federal Food, Drug and Cosmetic Act (FFDCA) and the Code of Federal Regulations (CFR).

**Paperwork Reduction Act Statement** - A Federal agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. The OMB numbers for this information collection are 0910-0032 (expires 6/30/2013) and 0910-0669 (expires 10/31/2013). Send comments on any aspect of this collection of information, including suggestions for reducing this burden to:

cvmesubmitter@fda.hhs.gov or to

U.S. Food and Drug Administration
Center for Veterinary Medicine
Office of New Animal Drug Evaluation
Attn: ONADE eSubmitter Program, HFV-100
7520 Standish Place
Rockville, MD 20855

**Please note:** There are several icons within the software to help guide you. Most importantly, the yellow light bulb indicates additional instructions, definitions, and other helpful hints while blue dots indicates required fields. The red exclamation indicates critical required questions which must be answered in order to move forward through the submission.

| | |
|---|---|
| Document Type: ! * | Investigational New Animal Drug File (i) |

| | | |
|---|---|---|
| Is this submission for a currently established file or application? | * | ( ) Yes<br>(•) No |
| » Please enter your Document Number (maximum 6 numbers): | | |

## 2.0 Firm Information

| | | |
|---|---|---|
| Are you a U.S. Company? | * | (•) Yes<br>( ) No |

| Please enter Firm information | * |
|---|---|
| *Establishment Information* | |
| Establishment Name | Bayer HealthCare LLC Animal Health Division |
| *Address* | |
| Address | 12809 Shawnee Mission Pkwy<br>Shawnee, KS, 66216, US |
| Telephone Number | (913) 268-2000 |
| Fax Number | (913) 268-2075 |
| D&B D-U-N-S Number | 152266193 |

## 4.0 Responsible Official Information

| Please enter Responsible Official Information | * |
|---|---|
| *Contact Information:* | |
| Contact Name | Ms. Mary K. Hagler |
| Occupation Title | Regulatory Affairs Manager |
| Email Address | mary.hagler@bayer.com |
| *Address* | |
| Establishment Name | Bayer HealthCare LLC Animal Health Division |
| Address | 12809 Shawnee Mission Pkwy<br>Shawnee, KS, 66216, US |
| Telephone Number | (913) 268-2563 |
| Fax Number | (913) 268-2075 |
| D&B D-U-N-S Number | 152266193 |

## 5.0 Submitter Information

| | | |
|---|---|---|
| Is the Submitter the same person as the Responsible Official or U.S. Agent? | * | (•) Yes<br>( ) No |

| Please enter Submitter Information | |
|---|---|
| *Contact Information.* | |
| Contact Name | |
| Occupation Title | |
| Email Address | |
| *Address* | |
| Establishment Name | |
| Address | |
| Telephone Number | |
| Fax Number | |
| D&B D-U-N-S Number | |

## Section: Submission Type Selection (INAD)

### 6.0 Submission Type Code / Amendment Information I

| Message: | Submission Selection: |
|---|---|
| » | Please select the INAD Submission Type: !* |
| | Establish INAD File (A) |
| » | Please select the Submission Classification Code: !* |
| | Other: Unclassified (OT) |

| Please select the Review Division to which you are submitting *: |
|---|
| Division of Therapeutic Drugs for Food Animals (HFV-130) |

| Is this an amendment to pending information that was previously submitted to CVM? | ( ) Yes<br>( ) No |
|---|---|

## Section: Initial INAD Submission (I/A/OT)

### 1.0 General Information

**Establish Investigational New Animal Drug (INAD) File**

| Are you requesting that information in the INAD be publicly available? * | ( ) Yes (•) No |
|---|---|

» Please detail the scope of the disclosure or press the ADD (+) button to attach a File. The PDF file should meet the specifications as described in the FDA eSubmitter User Manual (link above).

### 2.0 Product Description

**Item: 1**

| Established Name (list all active pharmaceutical ingredients; maximum 100 characters): * |
|---|
| Pradofloxacin |
| Proprietary Name, if available (maximum 100 characters): |
| TBD |

| Pharmacological Category (maximum 50 characters): |
|---|
| Fluoroquinolone Antibiotic |

| Select the Dosage Form: | Solution |
|---|---|

» If Other; Unclassified is selected, please specify dosage form and variation (maximum 60 characters):

| Select the Dosage Form Variation: | Solution |
|---|---|

» If Other; Unclassified is selected, please specify dosage form and variation (maximum 60 characters):

| Select the Route of Administration: | Injection |
|---|---|

» If Other; Unclassified is selected, please specify route of administration and variation (maximum 60 characters):

| Select the Route of Administration Variation: | Intramuscular |
|---|---|

» If Other; Unclassified is selected, please specify route of administration and variation (maximum 60 characters):

| In what animal species/class will the product be evaluated (maximum 100 characters): * |
|---|
| Finishing swine |

| Proposed indication(s) for use, if known: |
|---|
| Treatment and control of swine respiratory disease. |

## 3.0 Supporting Information

Please review the specifications for file attachments in the FDA eSubmitter User Manual.

| | | |
|---|---|---|
| Are you submitting supporting information about the drug or drug product? * | (•) Yes ( ) No | |
| » | Please press the ADD (+) button below to attach the supporting information. Please provide the information in bookmarked Portable Document Format (.pdf) files. The PDF file(s) should meet the specifications as described in the FDA eSubmitter User Manual (link above). * | |
| | File Attachment | INAD Request |

## 4.0 Investigational Labeling

| | |
|---|---|
| I affirm that the appropriate investigational labeling required under 21 CFR 511.1(a) or (b) will be affixed to the investigational drug product for studies conducted under 21 CFR 511.1(a) or (b), respectively. | [√] |
| *Warning:* | *Failure to accept the above affirmation will result in the inability to process the new (J)!NAD file request.* |

## 5.0 Comments

Please review the specifications for file attachments in the FDA eSubmitter User Manual.

| | |
|---|---|
| » | If you have additional comments that you would like to include in this submission please press the ADD (+) button to attach a single PDF file that contains the information. The PDF file should meet the specifications as described in the FDA eSubmitter User Manual (link above). |
| | |

**Request for Establishment of an INAD for the Use of Pradofloxacin Injectable in Swine**

Bayer Animal Health is in the early stages of evaluating the use of pradofloxacin in swine and is requesting an INAD for that purpose. When appropriate, we will schedule a development plan meeting with the Agency to discuss this use.

Bayer Animal Health currently has INADs for the investigational use of pradofloxacin in cattle (10-767), dogs (10-790) and cats (11-022).

In addition, under NADA 141-344, pradofloxacin is approved in cats for the treatment of skin infections (wounds and abscesses) caused by susceptible strains of *Pasteurella multocida*, *Streptococcus canis*, *Staphylococcus aureus*, *Staphylococcus felis*, and Staphylo*coccus pseudintermedius*.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

I-012380-A-0000-OT

Bayer HealthCare LLC
Animal Health Division
Attention: Mary K. Hagler
Regulatory Affairs Manager
12809 Shawnee Mission Pkwy
Shawnee, KS 66216

Re: Request to open an investigational new animal drug (INAD) file

Dear Ms. Hagler:

In response to your request dated June 18, 2013, we have opened an investigational new animal drug (INAD) file for pradofloxacin injection. Pradofloxacin injection is proposed for the treatment and control of swine respiratory disease in finishing swine, when administered as an intramuscular injection.

For administrative purposes, you have been assigned file number INAD 012380 for the above referenced use. Please reference this number in all drug shipments and correspondence with us concerning the drug while it is under investigational use.

AUTHORIZATION FOR THE USE OF EDIBLE PRODUCTS

This letter does not authorize the use of edible products derived from animals treated with your investigational drug. In accordance with Title 21, Code of Federal Regulations (CFR), section 511.1(b)(5), you must request and be granted an authorization for slaughter from CVM before you can use the edible tissues from investigational animals treated with your unapproved drug. When you request a food use authorization for treated animals, the request should be in writing and should include the following information: species, age, and class; proposed maximum dose and duration of treatment; method of administration; preliminary toxicological and metabolic data; and a Material Safety Data Sheet for pradofloxacin injection. You may also propose the number of animals to be covered by the authorization and a suggested withdrawal time.

NOTICE OF CLAIMED INVESTIGATIONAL EXEMPTION

Sections 511.1(b)(3) and (4) require the sponsor to maintain certain records and to submit specific information prior to each shipment or other delivery of the drug for clinical investigation in animals. You may file the notice of the drug shipment electronically to the Center for Veterinary Medicine (CVM) using FDA's eSubmitter tool. Please refer to the Center's electronic submission information on the CVM website at http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/ElectronicSubmissions/default.htm. Alternatively, you can send one copy of the completed form to CVM.

You must maintain records showing the name and post office address of the investigator to whom the investigational new animal drug is shipped and the date, quantity, and batch or code mark of each shipment and delivery for a period of two years after such shipment and delivery. These records must be made available for inspection and copying upon our request.

INVESTIGATIONAL LABELING

The appropriate investigational labeling required under 511.1(a) or (b) must be affixed to your investigational drug product before shipping your drug product for studies conducted under 21 CFR 511.1(a) or (b), respectively. Affix the investigational label to each individual drug container.

ADDITIONAL COMMENTS

1. Use of an investigational new animal drug obligates you, as the sponsor, to comply with the requirements in 21 CFR Part 511. We recommend that you review those regulations for further information about your responsibilities.

2. Your investigational new animal drug must be manufactured, processed, packaged, and labeled in such a way as to maintain appropriate standards of identity, strength, quality, and purity as needed for safety and to give significance to investigations made with the drug.

3. In order for us to complete our files, the disposition of all investigational animals and unused drugs must be reported to this office.

4. Promptly report to this office any adverse reactions that may suggest significant safety hazards.

5. We recommend that you request a presubmission conference to discuss the requirements for approval of your product.

6. After you have determined your product's proposed proprietary name, we recommend you submit it for our comment.

7. As required by section 502(e) of the Federal Food, Drug, and Cosmetic Act, the established name of animal drug products must follow the US Pharmacopeia (USP) nomenclature structure. For drug products with an existing United States Pharmacopeial (USP) monograph, the monograph title, published in the USP National Formulary (USP-NF), is the official compendial (established) name. If a new drug product does not have an existing USP monograph, the established name is comprised of the following three components in conformity with USP nomenclature policy: drug substance (active moiety) name + route of administration + dosage form. Based on the information provided in your submission dated June 18, 2013, the established name of your proposed drug product is "pradofloxacin injection".

If you submit correspondence relating to this letter, you should reference the date and the principal submission identifier. If you have any questions or comments, please contact me at (240) 276-8341. You may also contact Dr. Phillip G. Turfle, Acting Leader, Antimicrobial Drugs Team, at (240) 276-8616.

Sincerely,

*{see appended electronic signature page}*
Cindy L. Burnsteel, DVM
Director, Division of Therapeutic
Drugs for Food Animals
Office of New Animal Drug Evaluation
Center for Veterinary Medicine

## Electronic Signature Addendum for Submission ID

I-012380-A-0000-OT

| Signing Authority (Role) | Letter Date |
| --- | --- |
| Cindy Burnsteel (Division Director) | 9/17/2013 |

**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**

# Exhibit H

INAD 012-380, 10-767
Pradofloxacin Injectable Solution for Swine and Cattle

| Date | Subject |
|---|---|
| 06/27/2000 | Assignment of the INAD number. INAD 10-767 (cattle). |
| 09/17/2013 | Assignment of the INAD number. INAD 012380 (swine). |
| 10/01/2013 | Request for Conference Development Plan Meeting (DPM), Cattle |
| 10/23/2013 | Report of plasma pharmacokinetics of pradofloxacin 20% injectable solution comparative study completed. |
| 11/19/2013 | Discuss with representatives of CVM regarding pradofloxacin injection indicated for the treatment of bovine respiratory disease (BRD). |
| 01/02/2014 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of November 19, 2013. |
| 01/14/2014 | Request for changes/clarifications to CVM's Memorandum of Conference summarizing the meeting of November 19, 2013. |
| 02/28/2014 | CVM letter enclosing the amended Memorandum of Conference summarizing the meeting of November 19, 2013. |
| 03/31/2014 | Request for Conference Effectiveness, Cattle |
| 06/25/2014 | Discuss with representatives of CVM regarding proposed pivotal effectiveness protocol for pradofloxacin injection for the treatment of bovine respiratory disease (BRD). |
| 06/30/2014 | Slaughter Authorization Request, Cattle |
| 07/24/2014 | Pivotal Effectiveness Study Protocol Submission, Cattle |
| 08/07/2014 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of June 25, 2014. |
| 08/21/2014 | Submission of Pharmcologic-Toxicologic Summary, Cattle |
| 08/27/2014 | Study - Proof of Concept, Swine |
| 09/24/2014 | TAS Study Protocol Submission, Cattle |
| 10/01/2014 | Slaughter Authorization Request Response, Cattle |
| 10/10/2014 | Pivotal Effectiveness Protocol CVM Concurrence, Cattle |
| 11/24/2014 | CVM Response to Pharmcologic-Toxicologic Summary, Cattle |
| 12/09/2014 | TAS Study Protocol CVM Concurrence, Cattle |
| 01/30/2015 | Slaughter Authorization Request, Swine |
| 03/31/2015 | Request for Conference DPM, Swine |
| 05/07/2015 | Slaughter Authorization Request Response, Swine |
| 05/27/2015 | Discuss with representatives of CVM regarding pradofloxacin 20% injectable solution in swine for the treatment of swine respiratory disease (SRD). |
| 06/01/2015 | Safety evaluation (GSP) of pradofloxacin in piglets completed. |
| 07/10/2015 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of May 27, 2015. |
| 07/29/2015 | Request for Conference Microbiological Acceptable Daily Intake (mADI) Discussion, Cattle and Swine |
| 08/17/2015 | Effectiveness Study Protocol Submission, Swine |
| 11/05/2015 | Discuss with representatives of CVM regarding proposed development plan for pradofloxacin 20% injectable solution for the treatment of respiratory disease in cattle and in swine. |
| 11/10/2015 | Request for Conference Target Animal Safety (TAS, bull calves), Cattle |
| 12/03/2015 | Report of pivotal clinical efficacy study of pradofloxacin injectable solution for the treatment of bovine respiratory disease completed. |
| 12/14/2015 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of November 5, 2015. |
| 12/16/2015 | Pilot ADME, Cattle |
| 12/21/2015 | Pilot ADME, Swine |
| 12/21/2015 | Effectiveness Technical Section Submission, Cattle |

| | |
|---|---|
| 01/07/2016 | Discuss with representatives of CVM regarding plan to perform an adjunct modified target animal safety study to evaluate the effects of pradofloxacin on specific tissues of the bovine male reproductive tract. |
| 01/07/2016 | Pivotal safety study of 20% pradofloxacin injectable solution following subcutaneous administration to cattle completed. |
| 01/21/2016 | Effectiveness Protocol CVM Concurrence, Swine |
| 02/08/2016 | TAS Technical Section Submission, Cattle |
| 02/19/2016 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of January 7, 2016. |
| 03/10/2016 | Submission of Pharmcologic-Toxicologic Summary, Swine |
| 03/18/2016 | Request for presubmission conference to discuss development of pradofloxacin injectable solution for the treatment of respiratory disease in cattle and swine. |
| 05/18/2016 | Discuss with representatives of CVM regarding information to be submitted in the Chemistry, Manufacturing, and Controls Technical Section for the Pradofloxacin Injection drug product. |
| 05/31/2016 | Request for review of proprietary names. |
| 06/10/2016 | Submission of HFS Expert Statement, Guidance for Industry (GFI) 159 |
| 06/13/2016 | Amend Food Use Authorization (Change to Citric Acid Formulation), Swine |
| 06/17/2016 | Technical Section Complete (TSC) Effectiveness (P-0035), Cattle |
| 06/17/2016 | CVM Response to Pharmcologic-Toxicologic Summary, Swine |
| 06/21/2016 | Amend Slaughter Authorization (TAS bulls), Cattle, and Change to Citric Acid Formulation |
| 06/28/2016 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of May 18, 2016. |
| 07/11/2016 | Request for Categorical Exclusion, Cattle |
| 07/13/2016 | mADI Study Protocol Submission |
| 07/14/2016 | Justification of 2-Day Dosing in TAS, Swine |
| 08/01/2016 | TSC TAS Steer-Heifer (P-0036), Cattle |
| 08/04/2016 | Request for Categorical Exclusion, Swine |
| 08/08/2016 | TAS Study Protocol Submission, Swine |
| 08/29/2016 | mADI Protocol CVM Concurrence |
| 08/31/2016 | Comments in response to the proposed proprietary names. |
| 09/08/2016 | CVM Response to Amend Slaughter Authorization, Swine |
| 09/09/2016 | CVM Response to Amend Slaughter Authorization, Cattle |
| 09/20/2016 | Submission of information to establish the toxicological acceptable daily intake of pradofloxacin. |
| 09/23/2016 | Submission of 14C (Hot) Metabolism/Residue Study, Cattle |
| 12/01/2016 | Concurrence on HFS Expert Statement, Guidance for Industry (GFI) 159 |
| 12/12/2016 | Submission of Risk Assessment (RA) for Bacteria of Human Health Concern |
| 12/16/2016 | TAS Bull Calf Study Protocol Submission, Cattle |
| 12/29/2016 | Total and Comparative Metabolism Submission, Swine |
| 01/06/2017 | TSC Environmental Impact, Cattle |
| 02/17/2017 | TAS Study Protocol Submission, Swine |
| 02/24/2017 | Residue Metabolism Incomplete, Cattle and Swine |
| 04/04/2017 | TAS Protocol CVM Concurrence, Swine |
| 04/19/2017 | TAS Bull Calf Protocol CVM Concurrence, Cattle |
| 07/13/2017 | Study - Method Validation, Cattle |
| 08/17/2017 | Development report on the formulation of the pradofloxacin trihydrate injectable solution completed. |
| 09/12/2017 | ToxADI Complete, Cattle |
| 10/12/2017 | Report of pharmaceutical development of 22.73% pradofloxacin trihydrate injectable solution as drug product completed. |
| 10/26/2017 | Request to Bridge toxADI, Swine |
| 10/26/2017 | Request to Bridge mADI, Swine |
| 11/09/2017 | Microbial Food Safety Complete (Antimicrobial Resistance), Cattle |
| 12/11/2017 | Residue Metabolism Submission, Swine |

| | |
|---|---|
| 01/09/2018 | Request for Conference CMC, Cattle and Swine |
| 01/11/2018 | Report of manufacturing process development of pradofloxacin trihydrate drug substance completed. |
| 01/29/2018 | Microbiological Qualitative Risk Assessment, Swine |
| 02/12/2018 | Environmental Impact TSC, Swine |
| 02/28/2018 | Discuss with representatives of CVM regarding a proposed change to the manufacturing process of pradofloxacin. |
| 03/23/2018 | Proposal for mADI Accepted, Cattle |
| 04/13/2018 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of February 28, 2018. |
| 04/18/2018 | Request for changes/clarifications to CVM's Memorandum of Conference summarizing the meeting of February 28, 2018. |
| 04/18/2018 | Proposal for mADI Accepted, Swine |
| 04/20/2018 | ToxADI Complete (P-0044, P-0048), Swine |
| 04/23/2018 | Microbial Food Safety (Effect of Residues on Human Intestinal Flora) Complete, Cattle and Swine |
| 05/07/2018 | CVM letter indicating that the request clarification has been noted in the INAD files. |
| 07/20/2018 | Microbial Food Safety (Antimicrobial Resistance) Complete, Swine |
| 07/25/2018 | Discuss with representatives of CVM regarding data collected from the pivotal field effectiveness study and the organization of the future final study report. |
| 09/04/2018 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of July 25, 2018. |
| 11/28/2018 | Study - Residue Depletion, Cattle |
| 12/20/2018 | Study - Residue Depletion, Swine |
| 01/24/2019 | Trihydrate VMF Submission |
| 01/25/2019 | Original submission of pradofloxacin trihydrate to the Type II Veterinary Master File (VMF) (006293). |
| 01/25/2019 | Submission of study data regarding general information of pradofloxacin trihydrate and bioactivity data. |
| 02/19/2019 | Residue Depletion Study Protocol Submission, Swine |
| 03/27/2019 | Residue Depletion Protocol CVM Concurrence, Swine |
| 05/07/2019 | Study - Method Validation, Cattle |
| 07/23/2019 | CVM letter requesting additional data for VMF (006293). |
| 11/19/2019 | Target Animal Safety TSC (P-0065), Swine |
| 12/20/2019 | Target Animal Safety TSC (P-0084), Cattle |
| 01/30/2020 | Target Animal Safety TSC (P-0086), Cattle |
| 02/12/2020 | Target Animal Safety TSC (P-0070), Swine |
| 05/29/2020 | Effectiveness TSC (P-0072), Swine |
| 07/28/2020 | Discuss with representatives of CVM regarding Applicant's questions on the adjustment of the method SOP calibration range for the analysis of pradofloxacin in kidney tissue. |
| 08/03/2020 | Study - Supplemental Method Validation, Cattle |
| 08/18/2020 | Study - Residue Depletion, Cattle |
| 09/08/2020 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of July 28, 2018. |
| 09/11/2020 | Study - Residue Depletion, Swine |
| 10/12/2020 | Veterinary Master File (VMF) (006293) submission in response to CVM letter dated 2019-07-23, with stability data of pradofloxacin trihydrate attached. |
| 10/28/2020 | Discuss with representatives of CVM regarding a proposed regulatory method (LC-MS/MS) for the determination and confirmation of pradofloxacin residues in bovine kidney. |
| 11/02/2020 | Effectiveness TSC (P-0092), Cattle |
| 11/02/2020 | Effectiveness TSC (P-0078), Swine |
| 12/17/2020 | Study - Method Validation, Swine |
| 01/30/2021 | Request for meeting to discuss the method SOP and acceptability of data. |

| | |
|---|---|
| 02/04/2021 | Discuss with representatives of CVM regarding method SOP for the proposed regulatory method (LCMS/MS) for determination and confirmation of pradofloxacin in bovine kidney, and method trial study protocol. |
| 02/08/2021 | Discuss with representatives of CVM regarding the method SOP for the proposed regulatory method (LCMS/MS) for determination and confirmation of pradofloxacin in bovine kidney, and method trial study protocol. |
| 02/16/2021-02/18/2021 | Discuss with representatives of CVM regarding the performance and results from the then on-going live-video method demonstration of the pradofloxacin method. |
| 03/25/2021 | CVM letter enclosing the Memorandum of Conference summarizing the meetings of February 4, 2021, February 8, 2021, and February 16-18, 2021. |
| 08/10/2021-08/11/2021 | Discuss with representatives of CVM regarding the method SOP for the proposed regulatory method (LCMS/MS) for determination and confirmation of pradofloxacin in swine kidney, and method trial study protocol. |
| 08/12/2021 | CMC TSC, Cattle |
| 08/17/2021-08/18/2021 | Discuss with representatives of CVM regarding the performance and results from the then on-going live-video method demonstration of the pradofloxacin method. |
| 08/19/2021 | Residue Depletion Submission, Cattle |
| 08/24/2021 | CMC TSC, Swine |
| 09/29/2021 | CVM letter enclosing the Memorandum of Conference summarizing the meetings of August 10-11, 2021 and August 17-18, 2021. |
| 11/09/2021 | Study - Freezer Storage Stability, Swine |
| 02/11/2022 | Incomplete Letter Residue Depletion, Cattle |
| 03/29/2022 | Discuss with representatives of CVM regarding ongoing efforts to generate data to satisfy CVM's concerns regarding the freezer storage stability of pradofloxacin in cattle kidney. |
| 04/26/2022 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of March 29, 2022. |
| 05/12/2022 | Discuss with representatives of CVM regarding the pradofloxacin cattle cold residue depletion study. |
| 06/21/2022 | CVM letter enclosing the Memorandum of Conference summarizing the meeting of June 21, 2022. |
| 02/13/2023 | Freezer Storage Stability Submission, Cattle |
| 05/15/2023 | Study - Residue Depletion, Cattle |
| 05/15/2023 | Study - Residue Depletion, Swine |
| 08/11/2023 | CVM Response to Freezer Storage Stability Submission, Cattle |
| 11/08/2023 | Environmental Impact TSC, Cattle and Swine |
| 11/17/2023 | Human Food Safety TSC, Cattle |
| 01/22/2024 | Human Food Safety TSC, Swine |
| 02/02/2024 | All Other Information TSC, Cattle and Swine |
| 02/02/2024 | Labeling TSC Complete, Cattle and Swine |
| 02/02/2024 | CVM provides final draft of FOI summary, Cattle and Swine |
| 02/15/2024 | Submission of NADA for cattle and swine. NADA 141-550. |
| 04/09/2024 | CVM letter approving NADA 141-550. |

# Exhibit I

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Jessica Monachello
Bayer HealthCare LLC
Patent Counsel, Animal Health
P.O. Box 390
Shawnee Mission, KS

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,323,213

FEB 15 2017

Dear Ms. Monachello:

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. 6,323,213 for a period of 1,668 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Food and Drug Administration
CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: VERAFLOX®
(pradofloxacin)
Docket No.: FDA-2013-E-1573

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

| | | | |
|---|---|---|---|
| (68) | PATENT NO. | : | 6,323,213 |
| (45) | ISSUED | : | November 27, 2001 |
| (75) | INVENTOR | : | Stefan Bartel et al. |
| (73) | PATENT OWNER | : | Bayer Intellectual Property GmbH |
| (95) | PRODUCT | : | VERAFLOX® (pradofloxacin) |

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 6,323,213 based upon the regulatory review of the product VERAFLOX® (pradofloxacin) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,668 days

from February 12, 2017, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156.

I have caused the seal of the United States Patent and Trademark Office to be affixed this 8th day of February 2017.

Michelle K. Lee

Michelle K. Lee
Under Secretary of Commerce for Intellectual Property
and Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Jessica Monachello
Bayer HealthCare LLC
Patent Counsel, Animal Health
P.O. Box 390
Shawnee Mission, KS

In Re: Patent Term Extension
Application for
U.S. Patent No. 6,323,213

DEC 14 2016

# NOTICE OF FINAL DETERMINATION

A determination has been made that U.S. Patent No. 6,323,213, which claims a method of using the animal drug product, a method of manufacturing the animal drug product and the animal drug product VERAFLOX® (pradofloxacin), is eligible for patent term extension under 35 U.S.C. § 156. The period of extension has been determined to be 1,668 days.

A single request for reconsideration of this final determination as to the length of extension of the term of the patent may be made if filed within one month of the date of this notice. Extensions of time under 37 CFR § 1.136(a) are not applicable to this time period. In the absence of such request for reconsideration, the Director will issue a certificate of extension, under seal, for a period of 1,668 days.

The period of extension has been calculated using the Food and Drug Administration determination of the length of the regulatory review period published in the Federal Register of December 10, 2015 (80 Fed. Reg. 76701). Under 35 U.S.C. § 156(c):

| | | |
|---|---|---|
| Period of Extension | = | RRP - PGRRP - DD - ½ (TP - PGTP)[1] |
| | = | 3,285 - 0- 0 - ½ (3,235 - 0) |
| | = | 1,668 days (4.6 years) |

Since the regulatory review period began November 12, 2003, after the patent issued (November 27, 2001), the entire regulatory review period has been considered in the above determination of the length of the extension period 35 U.S.C. § 156(c). No determination of a lack of due diligence under 35 U.S.C. § 156(c)(1) was made.

Neither the limitations of 35 U.S.C. § 156(g)(6) nor 35 U.S.C. § 156(c)(3) operate to reduce the period of extension determined above.

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[1] Consistent with 35 U.S.C. § 156(c), "RRP" is the total number of days in the regulatory review period, "PGRRP" is the number of days of the RRP which were on and before the date on which the patent issued, "DD" is the number of days of the RRP that the applicant did not act with due diligence, "TP" is the testing phase period described in paragraphs (1)(B)(i), (2)(B)(i), (3)(B)(i), (4)(B)(i), and (5)(B)(i) of subsection (g) of 35 U.S.C. § 156, and "PGTP" is the number of days of the TP which were on and before the date on which the patent issued, wherein half days are ignored for purposes of the subtraction of ½ (TP - PGTP).

Upon issuance of the certificate of extension, the following information will be published in the Official Gazette:

| | |
|---|---|
| U.S. Patent No.: | 6,323,213 |
| Granted: | November 27, 2001 |
| Original Expiration Date[2]: | February 12, 2017 |
| Applicant: | Stefan Bartel et al. |
| Owner of Record: | Bayer Animal Health GmbH |
| Title: | Possibly Substituted 8-Cyano-1-Cyclopropyl-7-(2,8-Diazobicyclo-(4.3.0)-Nonan-8-yl)-6-Fluoro-1,4-Dihydro-4.Oxo-3-Quinolin Ccarboxylic Acids And Their Derivativcs |
| Product Trade Name: | VERAFLOX® (pradofloxacin) |
| Term Extended: | 1,668 days |
| Expiration Date of Extension: | September 7, 2021 |

[2]Subject to the provisions of 35 U.S.C. § 41(b).

Any correspondence from applicant with respect to this matter should be submitted via the USPTO's EFS Web system and should be addressed as follows:

By mail: Mail Stop Hatch-Waxman PTE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450.

Telephone inquiries related to this determination should be directed to the undersigned at (571) 272-7755.

Mary C. Till
Senior Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: FDA, CDER, Office of Regulatory Policy
10903 New Hampshire Avenue,
Bldg. 51 Room 6250
Silver Spring MD 20993-0002

Attention: Beverly Friedman

RE: VERAFLOX®
(pradofloxacin)
Docket No.: FDA-2013-E-1573

# Exhibit J

# UNITED STATES
# SECURITIES AND EXCHANGE COMMISSION
**Washington, D.C. 20549**

# Form 10-K

**☒ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
**For the fiscal year ended December 31, 2023**

**Commission file number 001-38661**


# Elanco Animal Health Incorporated

(Exact name of Registrant as specified in its charter)

| INDIANA | 82-5497352 |
|---|---|
| (State or other jurisdiction of incorporation or organization) | (I.R.S. Employer Identification No.) |

2500 INNOVATION WAY, GREENFIELD, INDIANA 46140
(Address and zip code of principal executive offices)

Registrant's telephone number, including area code (877) 352-6261

Securities registered pursuant to Section 12(b) of the Act:

| Title of each class | Trading Symbol(s) | Name of each exchange on which registered |
|---|---|---|
| Common Stock, no par value | ELAN | New York Stock Exchange |

Securities registered pursuant to Section 12(g) of the Act:

None.

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act.

Yes ☒ No ☐

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.

Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports) and (2) has been subject to such filing requirements for the past 90 days.

Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files).

Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company or an emerging growth company. See the definitions of a "large accelerated filer," "accelerated filer," "smaller reporting company" and "emerging growth company" in Rule 12b-2 of the Exchange Act.

| | |
|---|---|
| Large accelerated filer ☒ | Accelerated filer ☐ |
| Non-accelerated filer ☐ | Smaller reporting company ☐ |
| | Emerging growth company ☐ |

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☒

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act).

Yes ☐ No ☒

Aggregate market value of the common equity held by non-affiliates computed by reference to the price at which the common equity was last sold as of June 30, 2023, the last business day of the Registrant's most recently completed second fiscal quarter, was approximately $4.9 billion. The registrant has no non-voting common stock.

The number of shares of common stock outstanding as of February 21, 2024 was 492,970,011.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive proxy materials for its 2024 Annual Meeting of Shareholders are incorporated by reference into Part III hereof.

ELANCO ANIMAL HEALTH INCORPORATED
FORM 10-K
FOR THE YEAR ENDED DECEMBER 31, 2023
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## FORWARD-LOOKING STATEMENTS AND RISK FACTOR SUMMARY

This Annual Report on Form 10-K (Form 10-K) includes forward-looking statements within the meaning of the federal securities laws. These forward-looking statements include, without limitation, statements concerning the impact on Elanco Animal Health Incorporated and its subsidiaries (collectively, Elanco, the Company, we, us or our) caused by the integration of business acquisitions, expected synergies and cost savings, product launches, global macroeconomic conditions, expectations relating to liquidity and sources of capital, our expected compliance with debt covenants, cost savings, expenses and reserves relating to restructuring actions, our industry and our operations, performance and financial condition, and including, in particular, statements relating to our business, growth strategies, distribution strategies, product development efforts and future expenses.

Forward-looking statements are based on our current expectations and assumptions regarding our business, the economy and other future conditions. Because forward-looking statements relate to the future, by their nature, they are subject to inherent uncertainties, risks and changes in circumstances that are difficult to predict. As a result, our actual results may differ materially from those contemplated by the forward-looking statements. Important risk factors that could cause actual results to differ materially from those in the forward-looking statements include regional, national or global political, economic, business, competitive, market and regulatory conditions, including but not limited to the following:

- operating in a highly competitive industry;
- the success of our research and development (R&D) and licensing efforts;
- the impact of disruptive innovations and advances in veterinary medical practices, animal health technologies and alternatives to animal-derived protein;
- competition from generic products that may be viewed as more cost-effective;
- changes in regulatory restrictions on the use of antibiotics in farm animals;
- an outbreak of infectious disease carried by farm animals;
- risks related to the evaluation of animals;
- consolidation of our customers and distributors;
- the impact of increased or decreased sales into our distribution channels resulting in fluctuation in our revenues;
- our dependence on the success of our top products;
- our ability to complete acquisitions and divestitures and successfully integrate the businesses we acquire;
- our ability to implement our business strategies or achieve targeted cost efficiencies and gross margin improvements;
- manufacturing problems and capacity imbalances;
- fluctuations in inventory levels in our distribution channels
- risks related to the use of artificial intelligence (AI) in our business;
- our dependence on sophisticated information technology and infrastructure and the impact of breaches of our information technology systems;
- the impact of weather conditions, including those related to climate change, and the availability of natural resources;
- demand, supply and operational challenges associated with the effects of a human disease outbreak, epidemic, pandemic or other widespread public health concern;
- the loss of key personnel or highly skilled employees;
- adverse effects of labor disputes, strikes and/or work stoppages;
- the effect of our substantial indebtedness on our business, including restrictions in our debt agreements that limit our operating flexibility, changes in our credit ratings that lead to higher borrowing expenses and may restrict access to credit and changes in interest rates that may adversely affect our earnings and cash flows;
- changes in interest rates;
- risks related to the write-down of goodwill or identifiable intangible assets;
- the lack of availability or significant increases in the cost of raw materials;
- risks related to our presence in foreign markets;
- risks related to currency rate fluctuations;
- risks related to underfunded pension plan liabilities;
- our current plans not to pay dividends and restrictions on our ability to pay dividends;

- the potential impact that actions by activist shareholders could have on the pursuit of our business strategies;
- risks related to certain governance provisions in our constituent documents;
- risks related to tax expense or exposure;
- actions by regulatory bodies, including as a result of their interpretation of studies on product safety;
- the possible slowing or cessation of acceptance and/or adoption of our farm animal sustainability initiatives;
- the impact of increased regulation or decreased governmental financial support related to the raising, processing or consumption of farm animals;
- risks related to the modification of foreign trade policy;
- the impact of litigation, regulatory investigations, and other legal matters, including the risk to our reputation and the risk that our insurance policies may be insufficient to protect us from the impact of such matters;
- challenges to our intellectual property rights or our alleged violation of rights of others;
- misuse, off-label or counterfeiting use of our products;
- unanticipated safety, quality or efficacy concerns and the impact of identified concerns associated with our products;
- insufficient insurance coverage against hazards and claims;
- compliance with privacy laws and security of information; and
- risks related to environmental, health and safety laws and regulations.

See "Item 1A. Risk Factors" in Part I of this Form 10-K for a further description of these and other factors. Although we have attempted to identify important risk factors, there may be other risk factors not presently known to us or that we presently believe are not material that could cause actual results and developments to differ materially from those made in or suggested by the forward-looking statements contained in this Form 10-K. If any of these risks materialize, or if any of the above assumptions underlying forward-looking statements prove incorrect, actual results and developments may differ materially from those made in or suggested by the forward-looking statements contained in this Form 10-K. We caution you against relying on any forward-looking statements, which should also be read in conjunction with the other cautionary statements that are included elsewhere in this Form 10-K. Any forward-looking statement made by us in this Form 10-K speaks only as of the date hereof. Factors or events that could cause our actual results to differ may emerge from time to time, and it is not possible for us to predict all of them. We undertake no obligation to publicly update or to revise any forward-looking statement, whether as a result of new information, future developments or otherwise, except as may be required by law.

**SUBSIDIARIES OF THE COMPANY**
**EXHIBIT 21.1**

The following is a list of subsidiaries of the company as of December 31, 2023, omitting some subsidiaries which, considered in the aggregate, would not constitute a significant subsidiary.

| Subsidiary Name | Jurisdiction |
|---|---|
| Dista Products Limited | United Kingdom |
| EIO Insurance Company, Inc. | Tennessee (United States) |
| Elanco (Shanghai) Animal Health Co., Ltd. | China |
| Elanco (Shanghai) Animal Health Co., Ltd. – Beijing Branch | China |
| Elanco (Shanghai) Animal Health Co., Ltd. – Huang Pu Branch | China |
| Elanco (Sichuan) Animal Health Co., Ltd. | China |
| Elanco (Sichuan) Animal Health Co., Ltd. – Beijing Branch | China |
| Elanco (Taiwan) Animal Health Co. Ltd. | Taiwan |
| Elanco (Thailand) Ltd. | Thailand |
| Elanco AH Portugal, Unipessoal Lda | Portugal |
| Elanco Animal Health (Pty) Ltd. | South Africa |
| Elanco Animal Health GmbH | Germany |
| Elanco Animal Health Holdings BV | Netherlands |
| Elanco Animal Health Korea Ltd. | Korea |
| Elanco Animal Health Panama, S. De R.L. | Panama |
| Elanco Animal Health UK Limited | United Kingdom |
| Elanco Animal Vaccines Limited | United Kingdom |
| Elanco Australasia Pty Ltd – New Zealand Branch | New Zealand |
| Elanco Australasia Pty. Ltd. | Australia |
| Elanco Australia Holding Pty Ltd | Australia |
| Elanco Austria GmbH | Austria |
| Elanco Bangladesh Limited | Bangladesh |
| Elanco Belgium BV | Belgium |
| Elanco Brazil Holdings Ltda | Brazil |
| Elanco Canada Limited | Canada |
| Elanco Chile SpA | Chile |
| Elanco Colombia S.A.S. | Colombia |
| Elanco Costa Rica S.R.L. | Costa Rica |
| Elanco Denmark ApS | Denmark |
| Elanco Denmark ApS – Norway Branch | Norway |
| Elanco Denmark ApS – Sweden Branch | Sweden |
| Elanco Deutschland GmbH | Germany |
| Elanco Europe GmbH | Switzerland |
| Elanco Europe Ltd. | United Kingdom |
| Elanco Financing (Netherlands) B.V. | Netherlands |
| Elanco Financing S.A. | Switzerland |
| Elanco France S.A.S. | France |
| Elanco Global Holdings BV | Netherlands |
| Elanco GmbH | Germany |
| Elanco Hayvan Sağlığı Limited Şirketi | Turkey |
| Elanco Hong Kong Limited | Hong Kong |
| Elanco Hungary korlatolt felelossegu tarsasag | Hungary |
| Elanco India Private Limited | India |
| Elanco Innovation and Alliance Centre India LLP | India |

| | |
|---|---|
| Elanco International, Inc. | Indiana (United States) |
| Elanco Ireland Limited | Ireland |
| Elanco Italia S.p.A. | Italy |
| Elanco Japan K.K . | Japan |
| Elanco Malaysia Sdn Bhd | Malaysia |
| Elanco Missouri, Inc. | Delaware (United States) |
| Elanco Nederland B.V. | Netherlands |
| Elanco Netherlands Holding B.V. | Netherlands |
| Elanco New Zealand | New Zealand |
| Elanco Philippines Inc. | Philippines |
| Elanco Poland spółka z ograniczoną odpowiedzialnością | Poland |
| Elanco Rus Ltd. | Russia |
| Elanco S.R.L. | Argentina |
| Elanco Salud Animal S.A. de C.V. | Mexico |
| Elanco Saude Animal Ltda. | Brazil |
| Elanco Solution Center spółka z ograniczoną odpowiedzialnością | Poland |
| Elanco Spain, S.L. | Spain |
| Elanco SPEAR LLC | Delaware (United States) |
| Elanco Tiergesundheit AG | Switzerland |
| Elanco Tiergesundheit AG -- Austria Branch | Austria |
| Elanco Tiergesundheit AG -- Czech Branch | Czech |
| Elanco Tiergesundheit AG -- Egypt Representative Office | Egypt |
| Elanco Tiergesundheit AG -- Ho Chi Mihn City Representative Office | Vietnam |
| Elanco Tiergesundheit AG -- Lebanon Representative Office | Lebanon |
| Elanco Tiergesundheit AG -- Saudi Arabia Branch | Saudi Arabia |
| Elanco Tiergesundheit AG – South Africa Branch | South Africa |
| Elanco Tiergesundheit AG –Tunisia Representative Office | Tunisia |
| Elanco UK AH Limited | United Kingdom |
| Elanco US Inc. | Delaware (United States) |
| Elanco Veterina SVN d.o.o. | Slovenia |
| Elanco Vietnam Company Limited | Vietnam |
| Immuno-Vet Services (Pty) Ltd. | South Africa |
| Immunovet Services Zambia Ltd. | South Africa |
| Ivy Animal Health, Inc. | Delaware (United States) |
| KVP Pharma+Veterinar Produkte GmbH | Germany |
| Lohmann Animal Health (Malaysia) Sdn. Bhd | Malaysia |
| Lohmann Animal Health Beteiligungs GmbH | Germany |
| Lohmann Animal Health GmbH | Germany |
| Lohmann Animal Health International Inc. | Maine (United States) |
| Lohmann Animal Health Phils. Corp. | Philippines |
| Lohmann Animal Health S. A. (Pty) Ltd. | South Africa |
| Prevtec Microbia GmbH | Germany |
| Pt. Elanco Animal Health Indonesia | Indonesia |
| The Branch Office of Elanco Vietnam Company Limited in Dong Nai | Vietnam |
| The Representative Office of Elanco Vietnam Company Limited in Hanoi City | Vietnam |
| Vericore Limited | United Kingdom |