

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
9 September 2011 (09.09.2011)

PCT

(10) International Publication Number
WO 2011/107150 A1

(51) International Patent Classification:
A61K 31/5415 (2006.01) *A61P 29/00* (2006.01)

(21) International Application Number:
PCT/EP2010/052728

(22) International Filing Date:
3 March 2010 (03.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant (for all designated States except US):
BOEHRINGER INGELHEIM VETMEDICA GMBH
[DE/DE]; Binger Straße 173, 55216 Ingelheim am Rhein
(DE).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **GOWAN, Richard**
[AU/AU]; Boehringer Ingelheim GmbH, Corporate
Patents, Binger Straße 173, 55216 Ingelheim am Rhein
(DE).

(74) Agent: **HAMMANN, Heinz**; Boehringer Ingelheim
GmbH, Binger Straße 173, 55216 Ingelheim am Rhein
(DE).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,

AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ,
CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO,
DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT,
HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP,
KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD,
ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD,
SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR,
TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ,
TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV,
MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— as to non-prejudicial disclosures or exceptions to lack of
novelty (Rule 4.17(v))

Published:

— with international search report (Art. 21(3))

(54) Title: USE OF MELOXICAM FOR THE LONG-TERM TREATMENT OF MUSCULOSKELETAL DISORDERS IN
CATS

(57) Abstract: The invention is directed to the use of a formulation comprising meloxicam or a pharmacologically acceptable
meloxicam salt of an organic or inorganic base thereof for the long-term treatment of musculoskeletal disorders in cats. No nega-
tive effects on renal function occur following a treatment from 10 to 20 months or more.



WO 2011/107150 A1

Use of Meloxicam for the Long-term Treatment of Musculoskeletal Disorders in Cats

5

FIELD OF THE INVENTION

The present invention is directed to the long-term use of meloxicam to treat musculoskeletal disorders in cats with and without pre-existing renal disease
10 without any negative effects on renal function.

BACKGROUND OF THE INVENTION

Meloxicam is the only molecule licensed for treatment of chronic
15 musculoskeletal disorders in cats. These conditions affect the quality of life of cats and often require treatment. Impaired renal function is currently listed as a contraindication on NSAID data sheets. However, chronic renal disease and chronic musculoskeletal disorders, such as osteoarthritis (OA) are common in elderly cats and often coexist. Osteoarthritis affects synovial joints, associated
20 with loss of cartilage, inflammation, bone remodelling and formation of osteophytes. It is usually idiopathic and primarily affects elbow joints and hips. Clinical signs include for example difficulty in jumping, lameness, stiffness as well as behavioural changes such as demeanour, reduced grooming and resentment of handling.

25

Meloxicam was licensed for long-term use in cats in 2007 at an oral dose of 0.1 mg/ kg on day 1 followed by 0.05 mg/ kg. However, there is no prior art that demonstrates that the use of meloxicam is appropriate for long-term treatment of feline. It is reported by Gunew that feline suffering from osteoarthritis can be
30 treated with meloxicam in a concentration range between 0.01 – 0.03 mg/ kg. (Gunew et al., Long-term safety, efficacy and palatability of oral meloxicam at 0.01 – 0.03 mg/ kg for treatment of osteoarthritic pain in cats. Journal of Feline

Medicine and Surgery 2008, 10, 235-241) The trials were completed after a mean treatment duration of 5.8 months. However, since this study does not include any comparable placebo product and uses subjectivemeasurements only, its conclusions are questionable. A short-term (23 days) concept study
5 performed by Clarke & Bennett has also shown that a daily meloxicam dosage of 0.05 mg/ cat can be used to treat osteoarthritis. (Clarke & Bennett, Feline osterarthritis: a prospective study of 28 cases. Journal of Small Animal Practice 2006, 47, 439-445) This study does not include any thorough investigation and assessment of meloxicam treatment over a longer period of time.

10

Therefore, it is an object of the present invention to develop a long-term treatment of musculoskeletal disorders in cats, especially aged cats, with and without pre-existing renal disease and without accelerating the progression of renal diseases in cats.

15

DESCRIPTION OF THE INVENTION

Surprisingly, it has been found that meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base thereof may be used
20 for the long-term treatment of musculoskeletal disorders in cats, especially aged cats, with or without pre-existing renal disease, without having any negative effect on renal functions in cats during a treatment from 10 to 40 months or more.

Thus, the invention related to the use of meloxicam or a pharmacologically
25 acceptable meloxicam salt of an organic or inorganic base thereof for the preparation of a veterinary medical composition having analgesic efficacy for the long-term treatment of musculoskeletal disorders such as but not limiting to osteoarthritis in cats, particularly in older cats, without having any negative effects on renal functions during a treatment from 10 to 40 months or more.
30 Treatment with such a formulation will not accelerate already existing renal diseases in older cats, nor initiate any renal disease. According to the invention the pharmacologically acceptable meloxicam salt comprises the meglumine,

potassium or ammonium salt, preferably the meloxicam meglumine salt.

The present invention provides a formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base, one or more vehicles, and optionally one or more suitable additives, for the long term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more. Further the invention relates to the use of a formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more vehicles for preparing a veterinary medical composition having analgesic efficacy for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more. Said formulation contains or essentially consists of meloxicam or a pharmacologically acceptable salt thereof, water, optionally one or more additives selected from group of consisting of buffers, solubilisers, preservatives and optionally thickeners.

Meloxicam or a pharmacologically acceptable salt thereof for the long-term treatment of musculoskeletal disorders in cats having a pre-existing renal disease or having no pre-existing renal disease. Further, the invention relates to meloxicam or a pharmacologically acceptable salt thereof for the long-term treatment of musculoskeletal disorders in cats with chronic kidney disease. The musculoskeletal disease comprises but not limited to osteoarthritis.

The treatment occurs over a long-term period of at least 6 months, preferred ranges are selected from the group selected of 10 to 40 months, 10 to 37 months, 10 to 30 months, 10 to 25 months, 10 to 20 months, 10 to 17 months, 11 to 40 months, 11 to 37 months, 11 to 30 months, 11 to 25 months, 11 to 20 months, 11 to 17 months, 12 to 40 months, 12 to 37 months, 12 to 30 months, 12 to 25 months, 12 to 20 months, 12 to 17 months, 13 to 40 months, 13 to 37 months, 13 to 30 months, 13 to 25 months, 13 to 20 months, 13 to 17 months,

14 to 40 months, 14 to 37 months, 14 to 30 months, 14 to 25 months, 14 to 20 months and 14 to 17 months.

Older cats or aged cats are herein defined as being 5 years old or older, preferably from 5 to 20 years, even more preferably from 7 to 17 years, especially preferred from 10 to 13.4 to 15.5 to 16 years. Studies have shown that 53 % of cats over 7 years of age have renal diseases. Renal diseases may include acquired renal diseases such as chronic tubulo-interstitial nephritis, glomerulonephritis, pyelonephritis, amyloidosis, hydronephrosis, renal lymphoma or congenital diseases that cause kidney failure in cats such as polycystic kidney disease, renal aplasia, renal hypoplasia, renal dysplasia, amyloidosis. These may or may not be in a chronic disease state. However, the treatment is also appropriate for cats over 5 years of age without any pre-existing renal diseases.

In another embodiment the treatment of cats may be performed in a formulation useful for cats that are 5 years or older. The daily dose of the formulation is between 0.01 and 0.075 mg/kg daily, preferably 0.05 mg/kg. The lowest effective dose for a median maintenance dose was found to be 0.02 mg/kg. This range can be used to treat musculoskeletal disease such as osteoarthritis. The musculoskeletal disease is a chronic disease. The formulation contains or essentially consists of meloxicam salt, water, optionally one or more additives selected from the group consisting of buffers, solubilisers, preservatives and optionally thickeners.

Example

The medical records of a feline-only practice were searched for cats with OA being treated with meloxicam during a 4 year period. A diagnosis of OA was based upon any two of the following: owner noted mobility changes and/ or physical examination findings or radiographic changes. Cats included were older than 7 years and treated with meloxicam for a duration of more than 6

months. Complete medical records were available for review. Biochemistry, urinalysis and body weight were regularly monitored. The progression of renal disease in the aged non-renal and renal group treated was compared to age matched and IRIS matched untreated controls from the same clinic.

5

These results prove that a maintenance dose of 0.02 mg/kg meloxicam does not hasten progression of renal disease in aged cats or aged cats with pre-existent stable IRIS stage 1-3 renal disease. Therefore meloxicam can be used as a treatment for aged cats with painful musculoskeletal disorders and

10 concurrent renal disease. The aged cats treated with NSAID therapy shall be carefully monitored.

Materials and Methods

15 The database of a feline-only practice in suburban Melbourne was searched for cats which had been treated for chronic musculoskeletal disorders with meloxicam (Metacam oral suspension, Boehringer Ingelheim) during a 4 year period. The diagnosis of osteoarthritis or spondylosis deformans had been made based upon any two of the following: owner noted mobility changes,

20 physical examination findings or radiographic changes. The inclusion criteria included cats greater than 7 years old which had been treated continuously with meloxicam for a duration of more than 6 months and which had complete medical records available for review. In addition, cats were only included if serum biochemistry, urine analysis and body weight had been regularly

25 monitored.

Young cats were excluded, as were cats with no pre-treatment renal parameter measurements. In addition cats were also excluded if the owner could not be contacted to check that the cats were still receiving daily treatment with

30 meloxicam.

Age, breed, sex, concomitant diseases and medications as well as date treatment commenced, treatment duration and daily dose of meloxicam were recorded.

- 5 The presence or absence of pre-treatment renal disease and staging of the renal disease was carried out using plasma creatinine and urine specific gravity according to the following recognised International Renal Interest Society criteria (IRIS staging 2006):

www.iris-kidney.com

- 10 IRIS stage 1: Inadequate concentrating ability, abnormal renal palpation. Creatinine < 140 $\mu\text{mol/l}$ (< 1.6 mg/dL)

IRIS stage 2: Mild or absent clinical signs associated with renal disease. Creatinine 140-250 $\mu\text{mol/l}$ (1.6-2.8 mg/dL)

15

IRIS stage 3: Many clinical signs present. Creatinine 251-440 $\mu\text{mol/l}$ (2.8-5 mg/dL)

- 20 The treated cats were then subdivided into two groups: the renal treated group that belonged to IRIS stage 1-3 and were pre-treated, and the non-renal treated group that has no identifiable renal disease pre-treatment. Urine specific gravity, serum creatinine and bodyweight were used as indicators of renal disease progression. The progression of renal disease was then compared to age and IRIS matched untreated controls were then randomly identified from the
- 25 database of the same clinic.

Statistical Analysis

- 30 The median age of the renal and non-renal treated cats, median treatment duration and median maintenance dose was calculated.

The progression of renal disease in the non-renal treated group was compared to the age matched untreated controls. The progression of renal disease in the treated renal-diseased group was compared to age matched and IRIS matched untreated controls from the same clinic. Statistical analysis was carried out using a time adjusted area-under-the-curve (AUC) changes from baseline time 0 until the last recorded value (n).

$$AUC_{(0-n), adj} = \frac{AUC_{(0-n)}}{t_n - t_0} = \frac{\sum_{i=0}^n \frac{C_i + C_{i+1}}{2} (t_{i+1} - t_i)}{t_n - t_0}$$

10 t_0 : time point of first measurement (baseline)

t_n : time point of last measurement

C_i : difference of parameter concentration at time point $i=0, \dots, n$ to baseline

The Wilcoxon rank-sum-test was used to compare the groups. With this nonparametric test the distribution of the adjusted AUC of two groups was compared regarding the location. Under the null hypothesis it is assumed that there is no location shift in the distributions of the two treatment groups. If the resulting p-value is lower than the two-sided significance level of 5 % the null hypothesis is rejected.

20

Results

Out of a total database of 3016 cats, 214 cats which had been treated with Metacam® oral suspension were identified. Of these, 38 cats met the inclusion criteria for the treated group. 22 cats of these cats (58%) had IRIS stage 1-3 renal disease prior to treatment, whereof 8 cats were categorized to fit IRIS stage 1, 13 cats belonged to stage 2 and 1 cat was classified to belong to stage 3. 16 cats had no identifiable renal disease prior to treatment.

The median age of the renal treated group was 15.5 years and the non-renal treated group was 13.4 years.

5 The median treatment duration was 527 days in the renal group and 400 days in the non-renal group. After dose titration to the lowest effective dose, the median maintenance dose was 0.02 mg/kg daily in both the renal treated and non-renal treated groups. There were no differences in the progression of renal parameters in the renal group treated with meloxicam versus the age and IRIS matched untreated renal group or the non-renal group treated with meloxicam
10 versus the non- renal group not treated with meloxicam.

Two renal-treated cats were excluded from analysis of creatinine changes from baseline as their pre-treatment sample was not carried out within 3 days of the start of treatment. There were no statistically significant differences in weight
15 loss or the loss of urine concentrating ability in the renal group treated with meloxicam versus the age and IRIS matched untreated renal group or the non-renal group treated with meloxicam versus the non- renal group not treated with meloxicam. Mean serum creatinine concentration increased statistically significantly less over time in the renal group treated with meloxicam than in the
20 renal untreated group.

Example

25 The following formulation may be used according to the invention but not limited to:

- 1) Metacam® Suspension Boehringer Ingelheim for Cats

Claims

1. Meloxicam or a pharmacologically acceptable meloxicam salt of an
5 organic or inorganic base thereof for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more.
2. Meloxicam or a pharmacologically acceptable salt thereof according to
10 claim 1, characterised in that the cats have a pre-existing renal disease.
3. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 2, characterised in that the cats have no pre-existing renal disease
15
4. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 3, characterised in that the cats have a chronic kidney disease.
- 20 5. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 4, characterised in that the daily dose is from 0.01 and 0.075 mg/kg daily.
6. Meloxicam or a pharmacologically acceptable salt thereof according to
25 any one of claims 1 to 5, characterised in that the daily dose is from 0.02 to 0.06 mg/kg daily.
7. Meloxicam or a pharmacologically acceptable meloxicam salt thereof according to any one of claims 1 to 6, characterised in that the daily dose is
30 0.05 mg/kg daily.

8. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 7, characterised in that the musculoskeletal disease is osteoarthritis.
- 5 9. Meloxicam or a pharmacologically acceptable salt thereof according to any one of claims 1 to 8, characterised in that the musculoskeletal disease is a chronic disease.
- 10 10. A formulation containing meloxicam or a pharmacologically acceptable meloxicam salt of an organic or inorganic base and one or more vehicles for the long-term treatment of musculoskeletal disorders in cats, characterised in that no negative effects on renal function occur during a treatment from 10 to 40 months or more.
- 15 11. A formulation according to claim 10, characterised in that it contains or essentially consists of meloxicam salt, water, optionally one or more additives selected from the group consisting of buffers, solubilizers, preservatives and optionally thickeners.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/052728

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/5415 A61P29/00

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, SCISEARCH, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/135505 A2 (FORMEVET S P A [IT]; FORMENTI ANDREA [IT]; FORMENTI FILIPPO [IT]) 29 November 2007 (2007-11-29) page 5, line 22 - page 6, line 3; claims -----	1-11
X	WO 2008/113149 A2 (OURO FINO PARTICIPACOES E EMPR [BR]; NETO DOLIVAR CORAUCCI [BR]) 25 September 2008 (2008-09-25) page 6, line 13 - page 8, line 5; claims ----- -/--	1-11



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

17 June 2010

Date of mailing of the international search report

01/07/2010

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Venturini, Francesca

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2010/052728

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GUNEW M N ET AL: "Long-term safety, efficacy and palatability of oral meloxicam at 0.01-0.03mg/kg for treatment of osteoarthritic pain in cats" JOURNAL OF FELINE MEDICINE AND SURGERY, WB SAUNDERS, LONDON, GB LNKD-DOI:10.1016/J.JFMS.2007.10.007, vol. 10, no. 3, 1 July 2008 (2008-07-01), pages 235-241, XP022690365 ISSN: 1098-612X [retrieved on 2008-04-28] discussion -----	1-11
A	ROBSON M ET AL: "Intrinsic acute renal failure (ARF) associated with non-steroidal anti-inflammatory drug (NSAId) use in juvenile cats undergoing routine desexing-16 cases 1998-2005" JOURNAL OF VETERINARY INTERNAL MEDICINE, LIPPINCOTT, PHILADELPHIA, US, vol. 20, no. 3, 3 May 2006 (2006-05-03), page 740, XP009134517 ISSN: 0891-6640 * abstract -----	1-11
X	CLARKE, S.P & BENNETT, D.: "Feline osteoarthritis: a prospective study of 28 cases" JOURNAL OF SMALL ANIMAL PRACTICE, vol. 47, August 2006 (2006-08), pages 439-445, XP002587628 page 440 central column, line 22-35 -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2010/052728

Patent document cited in search report		Publication date		Patent family member(s)		Publication date	
WO 2007135505	A2	29-11-2007	AU	2007253015	A1	29-11-2007	
			CA	2652537	A1	29-11-2007	
			EP	2018211	A2	28-01-2009	
			JP	2009537506	T	29-10-2009	
			US	2009325943	A1	31-12-2009	
WO 2008113149	A2	25-09-2008	BR	PI0700969	A	04-11-2008	