# Safety of the chewable formulation of meloxicam, ‘Meloxirin Chewable’, for dogs

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**Safety of the chewable formulation, ‘Meloxirin Chewable’ (Fujita Pharmaceutical Co., Ltd., Tokyo, Japan) with meloxicam as an active ingredient was evaluated for dogs. The product was developed as a generic drug from a flavored tablet formulation: ‘Metacam Chewable Tablets for dogs’ (Boehringer Ingelheim Animal Health Japan Co., Ltd., Tokyo, Japan). For this study, 24 dogs were assigned to four groups of six animals each: (A) unmedicated controls; (B) orally administered the remedy in a dosage of 0.2 mg active ingredient per kilogram of body weight once, and in a dosage of 0.1 mg/kg b.w. once a day for the following seven days; (C) orally administered one tablet of the placebo product once a day for eight successive days; and (D) orally administered ten tablets of the placebo product daily for eight successive days. No adverse effect was observed for any dog of any group in the general findings, or in results of hematological and blood chemical examinations during 14 days after the initial administration. ‘Meloxirin Chewable’, along with excipients accompanying the medication, was confirmed as safe for dogs.**

**Keywords:** chewable formulation, dog, excipient, meloxicam, safety evaluation.

## 1. Introduction

Meloxicam, 4-hydroxy-2-methyl-*N*-(5-methyl-2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, a compound of the oxicam class [28], has been used as a non-steroidal anti-inflammatory drug (NSAID) in human clinical medicine [7, 11, 18, 20] and in the veterinary field for such animals as dogs [2, 6, 23], domestic cats [3, 6, 12, 15], and cattle [21]. In veterinary medicine, several dosage forms of meloxicam have been produced for dogs, including tablets, suspensions for oral administration, and injections. Among the tablets, a plain tablet formulation was developed first, followed by a flavored tablet formulation. The latter product, named ‘Metacam Chewable Tablets for dogs’, is beef flavored, although its trade name uses the word ‘chewable’. These brand-name and generic products are produced by Boehringer Ingelheim. Subsequently, generic veterinary drugs of the flavored tablets described above, ‘Meloxirin Chewable 1.0’ and ‘Meloxirin Chewable 2.5’, came to be sold on the market in Japan in 2016 by a Japanese pharmaceutical company: Fujita Pharmaceutical Co., Ltd. These novel generic products are ‘real’ chewable formulations using beef ingredients (*not* beef flavor) among the excipients.

The definitions of generic drugs differ among countries [1]. In many countries including Japan, although the definition of generic drugs has not been specified clearly by ordinance [24], it has been generally accepted that generic drugs include the same active ingredient(s) at the same dose(s) and that they are administered by the same route as the brand-name drugs. Their indications, dosages, and administration routes fundamentally coincide with those of the brand-name drug to ensure equivalent

clinical efficacy. In other words, the generic drugs are expected to provide the same degree of quality, efficacy, and safety as the brand-name product. They can be described as therapeutically equivalent [8, 9].

Accordingly, the active ingredient(s) and dosage of the generic product are the same as those of the brand-name drug. However, the types and amounts of ingredients of the excipients of the generic drug are not necessarily the same as those of the brand-name drug. Furthermore, the dosage forms of the generic and brand-name drugs need not be identical as long as the administration route is the same [8, 9]. For example, the generic drug of meloxicam developed in Japan is a beef-based chewable formulation, whereas the original drug is a plain tablet and other generic drug is a flavored tablet.

In spite of complete conformity of the active ingredient(s), when the types and amounts of ingredients of the excipients differ between brand-name and generic drugs (or among generic drugs), aspects of their pharmacokinetics such as absorption, distribution, metabolism, and excretion can differ somewhat between the two drugs. As a consequence, efficacy and safety might differ within the range of 'equivalence'.

The chewable formulation of meloxicam, developed as a generic drug, differs from the brand-name drug and the other generic drug in the dosage form because its excipients include beef. The present research was undertaken to evaluate the safety for dogs of this generic drug, and especially that of its excipients.

## 2. Materials and Methods

2-1 Drugs and a placebo product

Chewable formulations containing meloxicam as the active ingredient, 'Meloxirin Chewable 1.0' and 'Meloxirin Chewable 2.5' (Fujita Pharmaceutical Co., Ltd., Tokyo, Japan) (Fig. 1), were tested. These remedies are of equal size, with about 12 mm diameter and about 0.32 g weight. Single tablets of 'Meloxirin Chewable 1.0' and 'Meloxirin Chewable 2.5' respectively contain 1.0 mg and 2.5 mg of meloxicam.

Sample placebo products were produced by the manufacturer to check the preferences of dogs for 'Meloxirin Chewable 1.0' and 'Meloxirin Chewable 2.5'. This sample product had about 13 mm diameter and about 0.43 g weight, consisting of the same excipient ingredients of the remedy, but without the active ingredient.

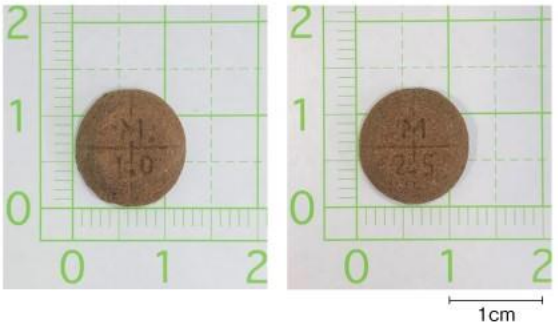


Fig. 1 Physical appearance of evaluated drugs, 'Meloxirin Chewable 1.0' (left) and 'Meloxirin Chewable 2.5' (right)

2-2 Animals

This study examined 24 privately owned dogs of various breeds in Japan. Of them, six had been regarded as medicated with meloxicam for some reason, although they had shown no severe symptoms. The 24 dogs were 11 females (seven of which had been ovariohysterectomized or ovariectomized) and 13 males (ten of which had been orchiectomized), aged 2–7 years, with 8.0–22.7 kg body weight.

The dogs were included in the research with each guardian's written consent. They were kept individually at their own residence during the research period without changing their living conditions, including food, from their normal regime. No veterinary procedure was conducted for the dogs, except for administration of the remedies and the placebo products.

2-3 Experimental procedure

This study was conducted with four test groups consisting of six dogs each: (A) unmedicated controls; (B) orally administered the remedy, basically in a dosage of 0.2 mg active ingredient per kilogram body weight once and in a dosage of 0.1 mg/kg b.w. once a day for the following seven days; (C) orally administered the placebo product in an amount of one tablet once a day for eight successive days; and (D) orally administered the placebo product in the amount of ten tablets daily for eight successive

Table 1 Administration of chewable formulations containing meloxicam as an active ingredient, 'Meloxirin Chewable 1.0', and 'Meloxirin Chewable 2.5' for dogs

| Dog No.[*1] | Body weight (kg)[*2] | Initial dose on the first day of treatment | | | Maintenance dose on and after the second day of treatment | | |
|---|---|---|---|---|---|---|---|
| | | Product administered | Dose | | Product administered | Dose | |
| | | | mg/head | mg/kg | | mg/head | mg/kg |
| B-1 | 12.4 | 1 tablet of 2.5 mg size[*3] | 2.5 | 0.20 | 1/2 tablet of 2.5 mg size[*3] | 1.25 | 0.10 |
| B-2 | 19.3 | 4 tablets of 1.0 mg size | 4.0 | 0.21 | 2 tablets of 1.0 mg size | 2.0 | 0.10 |
| B-3 | 22.4 | 2 tablets of 2.5 mg size | 5.0 | 0.22 | 1 tablet of 2.5 mg size | 2.5 | 0.11 |
| B-4 | 8.0 | 2 tablets of 1.0 mg size | 2.0 | 0.25 | 1 tablet of 1.0 mg size | 1.0 | 0.13 |
| B-5 | 11.8 | 1 tablet of 2.5 mg size[*3] | 2.5 | 0.21 | 1/2 tablet of 2.5 mg size[*3] | 1.25 | 0.11 |
| B-6 | 22.7 | 2 tablets of 2.5 mg size | 5.0 | 0.22 | 1 tablet of 2.5 mg size | 2.5 | 0.11 |

[*1] Dogs belonging to Group B in Tables 2-4
[*2] On the day 0 in Table 2
[*3] A different dose from that recommended by the manufacturer, because it is more suitable.

days.

The clinically healthy 18 dogs, other than those which need meloxicam treatment, were put into a replicate consisting of three animals each in order of introduction to the research. The three dogs of each replicate were then assigned randomly to groups A, C, and D. The six dogs of meloxicam-treatment, by contrast, were assigned to group B in each replicate in order. Each treatment was done for each dog of the respective group.

Administration of the meloxicam remedy to dogs of the medicated group was done at the dosage recommended by the manufacturer for the respective body weights of the dogs. These recommended dosages were defined based on the standard dosage of meloxicam to dogs, i.e., 0.2 mg/kg b.w. at initial administration on the first day and 0.1 mg/kg at maintenance on and after the second day. However, when a more suitable dosage than the recommendation by the manufacturer was found, the proper dosage was adopted. Each dose of meloxicam administered to the dogs of the group in which the meloxicam remedy was administered was eventually 2.0–5.0 mg/head or 0.20–0.25 mg/kg b.w. for a dog at the initial administration on the first day of treatment, and 1.0–2.5 mg/head or 0.10–0.13 mg/kg b.w. at the maintenance administration on and after the second day of treatment (Table 1).

For administration of the remedy or placebo product, these were presented under the nose of a dog to encourage the dog to consume it voluntarily. However, when a dog did not voluntarily consume the remedy or placebo product after 30 s passage, coercive oral administration was planned.

General findings of each dog were observed every day from one day before the first day of administration (or corresponding day in dogs of unmedicated control group) to 14 days after the initial day of administration (or corresponding day in dogs of unmedicated control). For dogs of three groups administered with the remedy or its placebo product, feces were also observed carefully every day for three days after administration to ascertain whether these products were passed in undigested forms through their feces or not. Measurement of body temperature, heart rate and breathing rate and hematological and blood chemical examinations were conducted on days -1, 0, 1, 3, 7, 10, and 14 (day 0 = the first day of administration, day 7 = the final day of administration)

2-4 Measurements of body temperature, heart rate, and breathing rate

Body temperature was measured by inserting a clinical electronic thermometer (MC-171W; Omron Healthcare Co., Ltd., Kyoto, Japan) into the rectum of the dog. Heart rate and breathing rate were respectively measured by auscultating cardiac pulsation and by visualization of the abdominal region of each dog for one minute.

Table 2 Body temperature, heart rate, breathing rate, and body weight of the dog

| Parameter | Test group | Measurement (average±standard deviation) on day | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -1 | 0[*2] | 1[*2] | 3[*2] | 7[*2] | 10 | 14 |
| Body temperature (℃) | A | 38.2±0.4 | 38.2±0.4 | 38.2±0.5 | 38.1±0.3 | 38.4±0.3 | 38.3±0.4 | 38.3±0.4 |
| | B | 38.2±0.4 | 38.2±0.3 | 38.2±0.4 | 38.1±0.3 | 38.3±0.4 | 38.2±0.5 | 38.3±0.4 |
| | C | 38.2±0.4 | 38.1±0.4 | 38.2±0.3 | 38.2±0.2 | 38.2±0.3 | 38.1±0.3 | 38.1±0.3 |
| | D | 38.0±0.3 | 38.2±0.3 | 38.4±0.3 | 38.2±0.2 | 38.3±0.2 | 38.3±0.3 | 38.3±0.2 |
| Heart rate (/minute) | A | 83±6 | 85±7 | 85±9 | 85±5 | 84±7 | 85±7 | 85±7 |
| | B | 84±5 | 85±6 | 83±5 | 83±6 | 84±5 | 85±5 | 86±5 |
| | C | 85±5 | 84±5 | 85±5 | 83±5 | 86±5 | 84±4 | 84±4 |
| | D | 84±5 | 85±5 | 84±4 | 84±5 | 86±6 | 85±4 | 84±4 |
| Breathing rate (/minute) | A | 21±3 | 22±2 | 19±1 | 21±1 | 21±2 | 21±3 | 21±3 |
| | B | 22±3 | 21±2 | 20±2 | 21±1 | 20±1 | 20±2 | 20±2 |
| | C | 21±2 | 20±2 | 23±3 | 21±2 | 21±2 | 22±1 | 22±2 |
| | D | 21±2 | 20±2 | 19±2 | 20±2 | 20±1 | 20±1 | 20±2 |
| Body weight (kg) | A | 15.6±5.3 | 15.8±5.5 | 15.8±5.4 | 15.8±5.5 | 15.8±5.5 | 16.0±5.5 | 16.0±5.4 |
| | B | 16.3±5.7 | 16.1±5.6 | 16.2±5.6 | 16.3±5.8 | 16.2±5.7 | 16.2±5.6 | 16.3±5.6 |
| | C | 15.7±5.3 | 15.9±5.2 | 15.8±5.3 | 15.8±5.2 | 15.9±5.3 | 15.8±5.3 | 15.8±5.3 |
| | D | 15.3±4.6 | 15.5±4.6 | 15.4±4.6 | 15.6±4.6 | 15.4±4.3 | 15.5±4.6 | 15.5±4.5 |

[*1] Test Group A: Unmedicated control
B: Orally administered with 'Meloxirin Chewable' basically in a dose of 0.2 mg/kg at the first day and then basically in a dose of 0.1 mg/kg on days 2 to 7
C: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of one tablet for eight successive days
D: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of ten tablets for eight successive days
[*2] Immediately before administration of the remedy or its placebo product

2-5 Hematological examinations

Hematological examinations were done using an automated hematology analyzer (pocH-100iV Sysmex Corp., Hyogo, Japan) for whole blood samples treated with an anticoagulant, ethylenediaminetetraacetic acid dipotassium salt dihydrate (EDTA-2K) after collection from cephalic vein of left or right forelimb of the dogs. The measured hematological parameters were the erythrocyte count, hematocrit value, hemoglobin concentration, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), leukocyte count, and platelet count.

2-6 Blood chemical examinations

Blood chemical examinations were done using an automated clinical chemistry analyzer (Fuji Dri-Chem NX500V; Fujifilm Corp., Tokyo, Japan) for serum samples conventionally separated from the whole blood samples that had been collected from cephalic vein of left or right forelimb of the dogs. The measured blood chemical parameters were the total protein concentration, urea nitrogen concentration, glucose concentration, total cholesterol concentration, total bilirubin concentration, lactate dehydrogenase activity, aspartate aminotransferase activity, alanine aminotransferase activity, and alkaline phosphatase activity.

2-7 Statistical analysis

Measurement values of body weight, body temperature, heart rate, breathing rate, and each of hematological and blood chemical parameters among days in each group and those measurement values among test groups on each day were analyzed using Kruskal–Wallis tests and Dwass's multiple comparison tests at a significance level of 5%. All

Table 3 Hematological findings from the dogs

| Parameter | Test group | Measurement (average±standard deviation) on day | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -1 | 0[*2] | 1[*2] | 3[*2] | 7[*2] | 10 | 14 |
| Erythrocyte count ($\times10^4/\mu$L) | A | 656±49 | 663±45 | 662±45 | 662±47 | 661±50 | 659±50 | 657±49 |
| | B | 683±41 | 685±32 | 682±39 | 686±39 | 684±33 | 684±32 | 673±52 |
| | C | 670±51 | 667±48 | 665±57 | 662±55 | 672±54 | 668±57 | 668±58 |
| | D | 665±47 | 658±44 | 662±45 | 659±52 | 659±42 | 662±48 | 659±48 |
| Hematocrit value (%) | A | 47.2±4.9 | 47.7±4.6 | 47.8±4.9 | 47.6±4.5 | 47.6±4.9 | 47.5±4.7 | 47.3±4.8 |
| | B | 49.6±5.5 | 49.7±5.1 | 49.5±5.4 | 49.7±5.4 | 49.6±5.3 | 49.5±4.9 | 48.7±5.9 |
| | C | 48.2±5.1 | 47.8±4.6 | 47.7±5.5 | 47.5±5.2 | 48.3±5.1 | 47.9±5.5 | 47.9±5.6 |
| | D | 48.3±4.2 | 47.2±3.6 | 48.2±3.8 | 47.8±3.9 | 47.8±3.7 | 48.0±3.9 | 47.8±3.9 |
| Hemoglobin concentration (g/dL) | A | 14.2±1.7 | 14.3±1.5 | 14.2±1.5 | 14.3±1.6 | 14.3±1.6 | 14.2±1.6 | 14.1±1.5 |
| | B | 14.4±1.7 | 14.5±1.1 | 14.4±1.0 | 14.4±1.0 | 14.5±1.0 | 14.4±1.0 | 14.2±1.0 |
| | C | 14.4±1.5 | 14.3±1.4 | 14.3±1.4 | 14.1±1.3 | 14.5±1.5 | 14.4±1.5 | 14.3±1.5 |
| | D | 14.4±1.1 | 14.2±1.2 | 14.2±1.1 | 14.1±1.2 | 14.2±1.1 | 14.2±1.1 | 14.3±1.3 |
| Mean corpuscular volume (MCV) (fL) | A | 71.9±4.2 | 72.4±3.9 | 72.4±4.0 | 72.4±4.0 | 72.4±4.1 | 72.2±3.8 | 72.3±4.0 |
| | B | 72.5±4.6 | 71.9±4.9 | 72.1±4.7 | 71.9±4.7 | 72.0±4.9 | 72.1±4.6 | 72.0±4.8 |
| | C | 71.9±4.1 | 71.6±3.9 | 71.6±4.1 | 71.6±4.3 | 71.8±4.0 | 71.7±4.1 | 71.6±4.0 |
| | D | 72.8±4.7 | 72.6±4.4 | 73.0±4.3 | 72.7±4.7 | 72.6±4.5 | 72.7±4.7 | 72.6±4.8 |
| Mean corpuscular hemoglobin (MCH) (pg) | A | 21.6±1.7 | 21.5±1.6 | 21.5±1.5 | 21.7±1.5 | 21.7±1.6 | 21.5±1.6 | 21.5±1.4 |
| | B | 21.1±1.5 | 21.1±1.4 | 21.1±1.4 | 21.1±1.4 | 21.3±1.3 | 21.1±1.4 | 21.2±1.3 |
| | C | 21.6±2.5 | 21.6±2.5 | 21.7±2.5 | 21.5±2.5 | 21.7±2.6 | 21.7±2.6 | 21.5±2.5 |
| | D | 21.8±2.1 | 21.6±2.1 | 21.5±2.1 | 21.6±2.2 | 21.7±2.1 | 21.6±2.1 | 21.7±2.0 |
| Mean corpuscular hemoglobin concentration (MCHC) (g/dL) | A | 30.2±3.2 | 30.0±3.1 | 29.9±2.9 | 30.2±2.9 | 30.2±3.1 | 29.9±3.0 | 30.0±2.9 |
| | B | 29.1±2.1 | 29.2±1.8 | 29.2±2.0 | 29.2±1.9 | 29.5±1.9 | 29.3±1.7 | 29.3±1.9 |
| | C | 30.1±2.9 | 30.1±2.7 | 30.2±2.9 | 30.0±2.8 | 30.1±2.8 | 30.3±2.8 | 30.0±2.8 |
| | D | 30.0±2.8 | 29.8±2.6 | 29.5±2.5 | 29.7±2.9 | 29.9±2.4 | 29.7±2.6 | 30.0±2.4 |
| Leucocyte count ($\times10^2/\mu$L) | A | 98±17 | 96±16 | 96±16 | 99±18 | 99±17 | 99±19 | 99±18 |
| | B | 101±17 | 98±15 | 96±15 | 98±16 | 96±13 | 99±18 | 99±18 |
| | C | 98±19 | 199±17 | 96±17 | 98±17 | 97±16 | 98±17 | 98±17 |
| | D | 100±18 | 96±17 | 101±16 | 98±17 | 97±16 | 100±16 | 98±15 |
| Platelet count ($\times10^4/\mu$L) | A | 35.7±6.6 | 35.7±6.9 | 37.7±4.8 | 36.2±4.8 | 36.7±4.7 | 36.3±5.8 | 36.8±5.7 |
| | B | 34.6±7.4 | 35.5±6.1 | 33.1±6.6 | 34.6±5.0 | 34.3±5.1 | 34.3±6.5 | 34.1±7.1 |
| | C | 35.5±7.5 | 35.4±8.3 | 36.4±6.2 | 34.9±7.8 | 34.6±7.6 | 33.4±6.4 | 34.4±6.7 |
| | D | 34.7±7.6 | 34.9±6.0 | 33.5±5.8 | 33.8±5.7 | 34.0±5.3 | 32.8±6.5 | 34.8±6.2 |

[*1] Test Group A: Unmedicated control
B: Orally administered with 'Meloxirin Chewable' basically in a dose of 0.2 mg/kg at the first day and then basically in a dose of 0.1 mg/kg on days 2 to 7
C: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of one tablet for eight successive days
D: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of ten tablets for eight successive days

[*2] Immediately before administration of the remedy or its placebo product

statistical analyses were performed with EZR (ver. 1.52; Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (ver. 4.02; The R Foundation for

Table 4 Blood chemical findings from the dogs

| Parameter | Test group | Measurement (average±standard deviation) on day | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | -1 | 0[*2] | 1[*2] | 3[*2] | 7[*2] | 10 | 14 |
| Total protein concentration (g/dL) | A | 6.5±0.1 | 6.5±0.2 | 6.5±0.1 | 6.5±0.1 | 6.5±0.1 | 6.4±0.1 | 6.5±0.1 |
| | B | 6.5±0.2 | 6.6±0.2 | 6.5±0.2 | 6.6±0.2 | 6.5±0.2 | 6.5±0.2 | 6.5±0.1 |
| | C | 6.4±0.2 | 6.5±0.2 | 6.4±0.1 | 6.5±0.2 | 6.5±0.2 | 6.6±0.2 | 6.5±0.1 |
| | D | 6.6±0.2 | 6.5±0.3 | 6.4±0.2 | 6.5±0.1 | 6.5±0.2 | 6.4±0.2 | 6.5±0.1 |
| Urea nitrogen concentration (mg/dL) | A | 12±2 | 13±1 | 14±1 | 13±1 | 13±1 | 13±1 | 13±1 |
| | B | 14±1 | 13±1 | 14±1 | 14±1 | 14±1 | 14±1 | 14±1 |
| | C | 13±2 | 13±2 | 14±2 | 14±2 | 14±2 | 13±2 | 13±2 |
| | D | 13±1 | 13±2 | 14±1 | 14±2 | 14±3 | 14±2 | 14±1 |
| Glucose concentration (mg/dL) | A | 88±5 | 90±5 | 87±5 | 88±4 | 90±4 | 86±4 | 88±4 |
| | B | 88±6 | 87±4 | 86±5 | 86±3 | 87±5 | 85±5 | 86±4 |
| | C | 86±6 | 87±5 | 89±5 | 90±7 | 87±7 | 89±5 | 87±7 |
| | D | 88±4 | 89±7 | 88±7 | 89±5 | 89±6 | 90±6 | 88±6 |
| Total cholesterol concentration (mg/dL) | A | 167±18 | 168±14 | 168±16 | 164±11 | 165±14 | 166±11 | 166±11 |
| | B | 172±15 | 172±16 | 176±14 | 172±13 | 174±13 | 172±12 | 170±13 |
| | C | 174±15 | 173±18 | 172±21 | 170±17 | 172±19 | 172±17 | 175±18 |
| | D | 172±16 | 172±12 | 171±13 | 174±14 | 174±15 | 174±15 | 171±13 |
| Total bilirubin concentration (mg/dL) | A | 0.18±0.03 | 0.18±0.03 | 0.18±0.03 | 0.17±0.03 | 0.18±0.03 | 0.19±0.04 | 0.18±0.03 |
| | B | 0.18±0.04 | 0.17±0.04 | 0.17±0.04 | 0.18±0.04 | 0.18±0.03 | 0.19±0.05 | 0.18±0.03 |
| | C | 0.18±0.04 | 0.17±0.03 | 0.18±0.03 | 0.18±0.05 | 0.18±0.03 | 0.18±0.03 | 0.18±0.04 |
| | D | 0.18±0.04 | 0.19±0.04 | 0.19±0.05 | 0.19±0.06 | 0.19±0.04 | 0.19±0.04 | 0.19±0.04 |
| Lactate dehydrogenase activity (IU/L) | A | 111±23 | 111±24 | 112±27 | 113±26 | 111±29 | 110±31 | 109±29 |
| | B | 111±24 | 110±24 | 106±24 | 110±25 | 110±30 | 113±25 | 113±25 |
| | C | 116±29 | 109±27 | 113±29 | 109±28 | 111±28 | 111±27 | 114±28 |
| | D | 112±26 | 112±24 | 112±25 | 112±29 | 111±23 | 108±24 | 109±23 |
| Aspartate aminotransferase activity (IU/L) | A | 25±7 | 22±7 | 24±6 | 25±5 | 23±7 | 25±6 | 25±6 |
| | B | 25±7 | 26±8 | 26±9 | 26±9 | 26±7 | 27±8 | 27±7 |
| | C | 28±8 | 26±8 | 29±6 | 25±7 | 29±9 | 27±9 | 27±5 |
| | D | 26±7 | 27±7 | 27±8 | 28±6 | 28±8 | 26±6 | 27±6 |
| Alanine aminotransferase activity (IU/L) | A | 40±10 | 38±8 | 40±11 | 42±10 | 40±8 | 40±10 | 41±8 |
| | B | 38±9 | 38±12 | 35±9 | 38±9 | 38±11 | 39±8 | 37±10 |
| | C | 39±8 | 40±10 | 40±10 | 41±11 | 41±10 | 41±12 | 39±11 |
| | D | 40±10 | 41±8 | 41±10 | 39±6 | 40±6 | 41±6 | 40±7 |
| Alkaline phosphatase activity (IU/L) | A | 78±15 | 80±18 | 80±17 | 79±18 | 80±15 | 79±15 | 81±19 |
| | B | 79±20 | 82±17 | 80±17 | 81±18 | 78±15 | 79±13 | 81±15 |
| | C | 79±16 | 81±13 | 83±17 | 79±19 | 82±15 | 80±12 | 80±16 |
| | D | 80±19 | 80±16 | 81±16 | 81±16 | 80±12 | 81±16 | 82±18 |

[*1] Test Group A: Unmedicated control
B: Orally administered with 'Meloxirin Chewable' basically in a dose of 0.2 mg/kg at the first day and then basically in a dose of 0.1 mg/kg on days 2 to 7
C: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of one tablet for eight successive days
D: Orally administered with a placebo product of 'Meloxirin Chewable' in an amount of ten tablets for eight successive days

[*2] Immediately before administration of the remedy or its placebo product

Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions that are used frequently for biostatistics [13].

2-8 Ethics

The dogs, which participated in this research after the authors received each guardian’s consent in writing, were all treated with due consideration of animal welfare during the research based on the “Regulation for Animal Experimentation at the General Incorporated Association Katsuragi Institute of Life Sciences” (the first and second authors’ former affiliation) under approval by the Institutional Animal Care and Use Committee.

**3. Results**

3-1 Voluntary consumption of the remedies and their placebo products

All the dogs to which meloxicam remedy had been presented voluntarily consumed the drugs, even when a number of tablets were administered. None expelled a tablet from the mouth.

All the dogs of the two groups to which one or ten placebo products had been presented, also voluntarily consumed the product(s). Even when ten products were administered, all the products were consumed by the dogs. No dog expelled the placebo products at all.

Accordingly, no case of coercively oral administration occurred.

3-2 General findings

No dog in any test group showed changes in activity, motility, appetite, or other general finings. None developed tremors, vomiting, diarrhea, or other symptoms. Carefully executed fecal examination for three days after the administration revealed no excretion of the undigested remedy or placebo product.

No abnormal findings were observed in the hair coat or skin of the dogs. Such dermatological findings as a coarse hair coat, alopecia, and redness of the skin were observed in none of the dogs.

The body temperature, heart rate, and breathing rate of the dogs were maintained within a defined range of values regarded as a standard level. No remarkable change occurred in the body weight of the dogs during the observation period (Table 2).

3-3 Hematological findings

No hematological parameter showed significant changes in any dog of any of the four test groups (Table 3).

3-4 Blood chemical findings

No blood chemical parameter showed significant changes in any dog of any of the four test groups (Table 4).

**4. Discussion**

It is not always true that generic drugs contain the same excipients as brand-name drugs, but it is more likely to contain different excipients from the brand-name drugs. In addition, the dosage form of generic drugs might differ from those of brand-name drugs. When developing a generic drug of a tablet-type former drug, the figure or size of the generic drug might differ. For example, it might be smaller than the brand-name medication. It is furthermore possible that a generic drug uses a chewable formulation if the brand-name drug was produced as a plain or flavored tablet. Chewable formulations are designed to be taken voluntarily by animals. Therefore, chewable formulations are not only therapeutically equivalent to the brand-name drugs: they are also superior to those in terms of their convenience of administration.

The products evaluated in the present research, ‘Meloxirin Chewable 1.0’ and ‘Meloxirin Chewable 2.5’, were developed in a chewable formulation by a Japanese pharmaceutical company, as generic drugs of ‘Metacam 1.0 mg Chewable Tablets for dogs’ and ‘Metacam 2.5 mg Chewable Tablets for dogs’, which are flavored tablets. The evaluated ‘Meloxirin Chewable 1.0’ and ‘Meloxirin Chewable 2.5’, different from ‘Metacam 1.0 mg Chewable Tablets for dogs’ and ‘Metacam 2.5 mg Chewable Tablets for dogs’, use beef among their excipients to create ‘real’ chewable formulations. Accordingly, the possibility cannot be denied that a difference exists between beef-based chewable and beef-flavored drugs in terms of their efficacy and safety, especially of their safety, even within the range of ‘equivalence’.

Because the safety of the active ingredient meloxicam has been adequately demonstrated,

including the incidence of adverse effects [14, 16], in dogs through worldwide use over many years, the present research was executed mostly to evaluate the safety of the excipients of the remedy. Although the present safety evaluation of privately owned dogs was not so probing as that conducted during development of new drugs by manufacturers, the research findings can be regarded as confirming the safety of the remedy in veterinary clinical settings.

Results show that no abnormality was observed in general findings and among the hematological and blood chemical parameters in all dogs administered the remedy at a recommended dose and with one or ten tablets of the placebo product: The evaluated drug was confirmed to be safe in dogs also in terms of the excipients. Furthermore, no undigested drug was excreted into the feces of the dogs, which suggests that the dogs digested the drugs successfully.

Dogs that develop an allergic reaction to beef are infrequently observed [10, 17, 27]. However, regarding chewable formulations using beef as an excipient, beef-based chewable combination drugs of ivermectin and pyrantel embonate have been used safely for many years worldwide for prophylaxis of canine *Dirofilaria* infections and for elimination of roundworms and hookworms in dogs [4, 5, 19, 22, 25, 26]. Although beef allergies of dogs deserve attention in cases of prescription of beef-based chewable drugs, such chewable formulations are thought to have low potential for developing to become severe matter in cases of ordinary clinical veterinary care.

The palatability of dogs to the evaluated chewable formulation was apparently very high, as far as examined in the present research. All the dogs voluntarily consumed the remedy and its placebo product, even after ten placebo products had been administered.

From these findings, the authors conclude that the beef-based chewable formulation, ‘Meloxirin Chewable 1.0’ and ‘Meloxirin Chewable 2.5’, containing meloxicam as an active ingredient can be administered as safely to dogs as the brand-name drugs and the other generic drugs, with a higher degree of convenience.

## Conflicts of Interest

Hiroshi Kohriki and Kazuya Tsuchiya are employees of Fujita Pharmaceutical Co., Ltd.

## Refernces


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