The effects of firocoxib (Previcox™) in geriatric dogs over a period of 90 days

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ABSTRACT

The long-term use of non-steroidal anti-inflammatory agents in geriatric dogs with osteoarthritis has not been well studied in veterinary medicine. This study evaluated the effects of firocoxib administered to dogs over 7 years of age for 90 days. Pain and lameness scores were evaluated by the owner weekly for the 1st month and then biweekly through to the end of the study, the veterinarian evaluated the dogs monthly. Serum chemistry, including urea, creatinine, alanine transferase, aspartate transaminase, bile acids and bilirubin, urine specific gravity and a urine dipstick, were performed at monthly intervals. Forty-five dogs were enrolled into the treatment group and 9 into the control group. A total of 33 dogs completed the trial in the treatment group and 8 in the control group. Lameness and pain scores were found to be significantly lower in the treated group from day 30 for most parameters evaluated. Bile acids (although not comparable to controls, with higher mean value and a high standard deviation in the control group; in addition the control group had increased bile acids at day 0) and urea (within normal reference range provided (WNL)) were significantly different in the treatment group between days 0 and 90. Urea (WNL) on days 30 and 90 and creatinine (WNL) on day 90 were significantly different between the control group and the treatment group. The most common adverse events reported were diarrhoea, vomition, dark faeces and anorexia. This study showed that firocoxib was effective in managing pain associated with osteoarthritis for 90 days. Despite the geriatric high-risk population used for this study, minimal biochemical changes were seen and adverse drug events seen were in agreement with those previously reported.

Keywords: adverse events, canine, lameness, firocoxib, geriatric, long term, non-steroidal anti-inflammatory drugs, pain control.

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INTRODUCTION

Previcox™ (firocoxib) is a new generation non-steroidal anti-inflammatory drug (NSAID) that is highly COX-2 (cyclo-oxygenase 2 isoenzyme)-specific in dogs[18]. At an 80 % inhibition of cyclo-oxygenase enzymes it has a 427:1 affinity for COX-2[18]. It has been suggested that for an NSAID to exert its clinical effect an 80 % inhibition of the cyclo-oxygenase enzyme is required[13,14]. This makes Previcox a COX-2 specific drug in clinical practice and the 1st to be introduced onto the South African market for dogs.

Previcox has a half life of 7.59 hours and an oral bioavailability of 36.9 %[5]. In a randomised, placebo-controlled 4-period cross-over laboratory study involving 8 dogs conducted to confirm the effective analgesic dose of firocoxib in a synovitis model of arthritis, the firocoxib treatment group performed significantly better than placebo at 3 hours post-treatment and significantly better than the placebo and carprofen at the 7 hours post-treatment[9]. Improvement in lameness score was also significantly better in the dogs treated with firocoxib than placebo and carprofen at both 3 and 7 hours post-treatment[9]. The use of the highly selective COX-2 inhibitor firocoxib reduced acute pain due to synovitis and provided significant improvement in weight bearing at a dose of ≥5 mg/kg body weight[9]. These effects were better than those observed with carprofen and similar to those with vedaprofen[9]. At a therapeutic dose of 5 mg/kg almost no inhibition of COX-1 takes place.

The target population used in this study was a geriatric, high-risk population which inherently involves certain physiological changes associated with senior pets. The prevalence of chronic kidney disease in dogs increases with age, with 20 % of dogs between 7 and 10 years of age and 45 % more than 10 years of age having renal disease[21]. The actual incidence in a canine population is between 0.5–7 %[21]. With age there is a loss of renal mass and glomeruli and a decrease in renal blood flow[11]. Creatinine clearance decreases but serum creatinine remains normal due to a decrease in muscle mass and a decrease in urine SG[11]. NSAIDs are known to have a potential to influence renal function[15]. Hepatic mass also decreases with age[11]. There is a loss of functional reserve within the liver and this may become problematic[11]. The most common conditions diagnosed in geriatric patients undergoing routine screening before anaesthesia were neoplasia, chronic kidney disease and Cushing's disease[12].

From the literature, it is evident that NSAIDs are well tolerated in general in animals. The long-term effect of NSAIDs in geriatric dogs has, however, not been well studied. The age-related changes in organ function may predispose these patients to an increase in side-effects associated with NSAIDs. Osteoarthritis is a common condition in geriatric dogs requiring pain relief and is generally treated with NSAIDs. This study was undertaken to evaluate the effects of a 90-day administration of Previcox in geriatric dogs (dogs older than 7 years). The effects on pain and lameness as well as renal and liver function were evaluated.

MATERIALS AND METHODS

Forty-five dogs were enrolled in a treatment group (Group P) and 9 dogs in a control group (Group C). Group P dogs had to be older than 7 years of age and have a diagnosis of osteoarthritis in one or more joints, having not received any treatment in the last 3 months for this condition, free of systemic disease (cardiovascular, respiratory, renal, hepatic, gastrointestinal) and not currently receiving any medication for any specific disease. Group P dogs received a 90-day treatment with Previcox at the recommended dose according to weight. Group C consisted of a similar group of dogs except that no diagnosis of osteoarthritis was made and no treatment was required. Group C dogs received no treatment. No complementary medicines were allowed during the trial period.

On admission to the trial, the owner's

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informed consent was obtained. The owners were informed that they could withdraw their animal at any point during the study without giving a reason. The age, sex, breed and weight were recorded for each patient enrolled. No distinction was made on sterilisation status as very few of the animals were not sterilised. The veterinarian examined the dog to determine the overall health and well-being of the dog before entering the trial. Attention was given to the cardiovascular, respiratory, gastrointestinal and renal systems. Dogs with heart disease, respiratory disease, gastric ulceration and renal failure were excluded from the study. Acute infectious arthritis was excluded from admission to the study. The veterinarian was required to accurately make the diagnosis of osteoarthritis using confirmatory tests as required. The joint or joints affected were recorded as well as the method of diagnosis.

The veterinarian evaluated the dog's clinical signs associated with osteoarthritis using the following parameters: overall lameness, pain on palpation/manipulation (most severely affected limb) and range of motion (most severely affected limb). This was scored according to Table 1 by the veterinarian on days 0, 30, 60 and 90. The owner evaluated the lameness and activity of the dog using a visual analogue scale. A simple 4-point scoring system was used to evaluate the dog's ability to climb stairs, rise from a resting position, stiffness after playing, limping, amount of time spent sleeping or lying and overall functionality. The 4-point scoring system is described in Table 2 The owner evaluated the dog on days 0, 7, 14, 21, 30, 45, 60, 75 and 90. These data were only collected for dogs in Group P.

A urine sample was obtained by the veterinarian. Urine specific gravity was recorded. A dipstick was used to record the presence of proteins, red blood cells, glucose and pH and the results recorded. All trace readings were scored as 1. A blood sample was taken and submitted to a veterinary pathology laboratory (Idexx Golden Vet, Sunninghill) for routine analysis. Urea, creatinine, alanine transferase (ALT), aspartate transaminase (AST), bile acids and bilirubin were determined for each sample submitted. Urine and serum chemistry was done on days 0, 30, 60 and 90 for dogs in group P and on days 0 and 90 for dogs in group C. Normal values for serum chemistry are given in Table 3.

A list of common clinical adverse events of non-steroidal anti-inflammatory drugs was provided to the owner. The list included: anorexia, depression, lethargy, increased urination (polyuria), increased water intake (polydypsia), bloody or dark tarry faeces. The owner was requested to record the number of times any of these side effects occurred or any other abnormality they detected during the course of the trial. If the owner suspected any of the adverse events (as listed in the monitoring sheet) to be due to the drug being administered they were instructed to discontinue the therapy and contact the veterinarian or study coordinator. When the owner felt that the pain was not being controlled by the trial drug at any time, codeine at 1–4 mg/kg administered 2–4 times daily was allowed, and recorded by the owners.

Data were entered into a spreadsheet (Excel, Microsoft Corporation, Redmond). Statistical analysis was performed using SigmaStat for Windows, (Jandel Corporation). Statistical significance was set at $P < 0.05$. Descriptive statistics were used to describe the populations in

Table 1: **Veterinarians' evaluation of lameness, pain and range of motion.**

Scoring system

Lameness
0 – No lameness
1 – Mild lameness (Occasional gait abnormality)
2 – Moderate lameness (obvious gait abnormality with/without occasional non-weight bearing)
3 – Severe lameness (consistently non-weight bearing)

Pain on manipulation/palpation
0 – No pain
1 – Slight pain (scarcely withdraws limb)
2 – Moderately painful (definitely withdraws limb)
3 – Severely painful (prominently withdraws limb)

Range of motion
0 – Normal
1 – Slightly reduced
2 – Moderately reduced
3 – Severely reduced

Table 2: **Owners' evaluation of pain in dogs.**

Parameter	Definition	Score
Reluctance to climb stair or hop into a car?	Cannot	0
	Can but very reluctantly	1
	Will do it	2
	Expedient	3
Rising from a resting position	Cannot	0
	Can but very reluctantly	1
	Will do it	2
	Expedient	3
Stiffness after playing	Cannot play	0
	Can play but very reluctantly	1
	Plays but tires	2
	Expedient	3
Degree of limping or lameness	All the time	0
	Often signs	1
	Occasional signs	2
	No signs	3
Amount of time spent sleeping or lying around	Sleeps all the time	0
	Inactive	1
	Moderate activity	2
	Normal activity	3
Over activity and functionality	Inactive	0
	Reluctant to be active	1
	Functionally active	2
	Active and lively	3

Table 3: **Normal values for serum chemistry.**

Parameter	Units	Normal range
Urea	mmol/ℓ	3.6–8.9
Creatinine	μmol/ℓ	100–130
ALT	U/ℓ	60–10
AST	U/ℓ	60–20
Bilirubin	μmol/ℓ	0–12
Bile Acids	μmol/ℓ	0–15

Groups P and C. The *t*-test was used to determine differences between groups P and C for age and weight. A Mann-Whitney rank sum test was used to determine the difference in group C between 0 and 90 days for rank data and the *t*-test for nominal data in the clinical pathology data. A 1-way analysis of variance was used to detect statistical differences in group P for clinical pathology data between the different days. When statistical difference was found, Dunn's method with day 0 as the control was applied to identify the days that were different. Group C combined data were compared to group P data using 1-way analysis of variance. When statistical difference was found, Dunn's method with group C data as the control was applied to identify the days that were different. The veterinarian's evaluation of lameness and the owner's evaluation of pain and activity were compared using 1-way analysis of variance on ranks. If statistical significance was found, Dunn's method was applied to identify days that were different using a pair-wise comparison.

RESULTS

A total of 45 forms were collected in the treatment group and 9 in the control group. In the treatment group, 3 owners provided incomplete data sheets. One owner did not provide the information on whether the animal preferred to sleep all day. One owner did not collect information on stair climbing beyond day 21. One owner only collected information to day 45, one to day 21 and one to day 60. One form was rejected because data were only collected at 0 and 30 days. One dog missed the day-30 check-up, but the remaining data were included. No urine was obtained from 1 dog on a single occasion (3rd sample) in the treatment group. No urine was obtained on 2 occasions from a control dog but the serum chemistry results were included. No urine was obtained on the 2nd occasion from a control dog. A single AST value from the baseline reading was not analysed for 1 treatment dog and the 1 control dog.

One control dog (2 years of age) and 3 treatment dogs (1 – 4 years; 2 – 5 years) were excluded as they were too young for inclusion. Two dogs were withdrawn from the study after the 1st blood sample due to grossly abnormal blood results (AST) in the treatment group. One dog was withdrawn from the trial by the owner on day 60 in the treatment group owing to poor appetite and weight loss. Two owners withdrew their dogs voluntarily owing to gastrointestinal side effects (diarrhoea) after 7 days and 60 days of treatment. Four dogs died in the treatment group due to conditions unrelated to the treatment. One dog died 17 days after starting treatment – the cause is unknown and the owner declined a *post mortem*. A 2nd dog died 14 days after starting treatment due to babesiosis. A 3rd dog was euthanased on humane grounds after 30 days of treatment and a 4th dog after 45 days of treatment. A total of 33 dogs in the treatment group and 8 dogs in the control group were analysed.

Table 4: **Demographics of Group C.**

	n
Breed	
Great Dane	1
Staffordshire bull terrier	1
Belgium shepherd	1
Spaniel	1
Labrador	1
Schnauzer	1
Dalmatian	1
Rottweiler	1
Sex	
Male	4
Female	4
Weight (kg)	32.64 ± 20.82
Age (years)	9.63 ± 2.07

Table 5: **Demographics of Group P.**

	n
Breed	
German shepherd dog	4
Staffordshire bull terrier	4
Cross breed	4
Boxer	3
Great Dane	3
Spaniel	2
Bearded collie	1
Belgium shepherd	1
Border collie	1
Bouvier	1
Bull mastiff	1
Doberman	1
Fox terrier	1
Labrador	1
Maltese	1
Miniature Schnauzer	1
Old English sheep dog	1
Rough collie	1
Whippet	1
Sex	
Male	11
Female	20
Not Stated	2
Weight (kg)	31.64 ± 17.26
Age (years)	9.83 ± 1.84

Table 6: **Sites of osteoarthritis in Group P.**

Osteoarthritis	*n*
Hip dysplasia	10
Stifle	9
Stifle and hips	6
Elbows	2
Hips and elbows	2
Elbows and lumbar spine	1
Lumbar spine	1
Shoulders and lumbar spine	1
Stifle and elbow	1

The demographics of the group C dogs are are given in Table 4 and of group P in Table 5. The control and treatment groups were not statistically different with respect to age and weight. The sites of osteoarthritis in group P is given in Table 6.

The veterinarians' evaluation of lameness score was statistically significantly different between days 0 and 60, 0 and 90 and 30 and 90, palpation score on days 0 and 30, 0 and 60 and 0 and 90, range of motion on days 0 and 60 and 0 and 90 and the overall score on days 0 and 30, 0 and 60 and 0 and 90. The owner evaluation of pain was statistically different between days 0 and 45, 0 and 60, 0 and 75, 0 and 90, 7 and 60, 7 and 75 and 7 and 90 and the activity score on days 0 and 45, 0 and 60, 0 and 75 and 0 and 90. This is graphically represented in Fig. 1. The dogs' ability to climb stairs, pain on rising, limping, sleeping and activity was signifi-

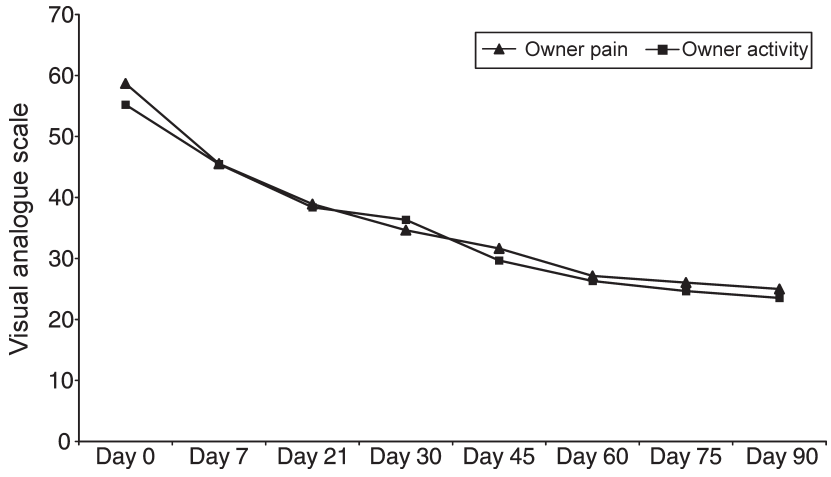

Fig. 1: **Owners' evaluation of activity and pain using a visual analogue scale.**

cantly different on days 0 and 30, 0 and 45, 0 and 60, 0 and 75 and 0 and 90. Stiff after playing was significantly different on days 0 and 45, 0 and 60 and 0 and 75.

The clinical pathology results for groups P and C are contained in Tables 7 & 8. No statistical difference was found between day 0 and day 90 in group C. Group C data for days 0 and 90 were combined for comparison to group P data. In group P, bile acids and urea were statistically different between days 0 and 90. A statistically significant difference was found between the combined data of group C and group P for creatinine at day 90 and urea at days 30 and 90.

Side effects were noted in 13 dogs with 27 adverse events recorded. Four dogs had a single event while the remaining dogs had more than 1 adverse event. One dog had 4 adverse events. This study covered a total of 2970 treatment days and this represents an adverse event rate of 0.009 % per day of treatment. The most common adverse events reported were diarrhoea, vomition, dark faeces and anorexia. The number and type of side effects recorded by owners during the study is reported in Table 9. No dogs received any codeine for uncontrolled pain.

DISCUSSION

This study should be interpreted in the light of the fact that it was conducted in patients older than 7 years of age. Geriatric patients are known to develop changes in hepatic and renal function that are age related. NSAIDs are commonly prescribed for osteoarthritis, which is common in geriatric patients, and these drugs are known to have effects on hepatic and renal function. The effects of NSAIDs have not been well studied in this group of patients, rendering the data collected here difficult to interpret.

Firocoxib has been evaluated in 6 healthy experimental dogs when administered for 28 days[25]. Complete blood count, urea, creatinine, alanine transaminase (ALT), alkaline phosphatise (ALP), gamma-glutamyltransferase (GGT), occult faecal blood, platelet function and mucosal bleeding time were measured on days 0, 7, 14, 21 and 29[25]. Urine analysis and gastroscopy were preformed on days 0 and 29[25]. No significant difference between measured values was shown over the 28 days[25]. The long-term effects of carprofen, etodolac, flunixin, ketoprofen and meloxicam have been studied in dogs[16,22]. This was performed in medium-sized dogs aged between 1 and 5 years of age[16]. A complete blood count, urea, creatinine, ALT, ALP, GGT, protein, albumin, globulin, bleeding time, clotting

Table 7: **Urine results for Groups P and C.** Urine RBC = urine red blood cells.

		Group P		Group C	
Parameter	**Day**	**Mean**	**SD**	**Mean**	**SD**
Urine specific gravity	0	1028.61	12.32	1027.86	4.95
	30	1035.03	12.91		
	60	1032.73	11.39		
	90	1035.50	13.44	1020.17	12.04
Urine pH	0	6.58	0.91	6.50	1.12
	30	6.25	0.92		
	60	6.47	1.11		
	90	6.12	0.86	6.50	1.22
Urine protein	0	0.58	0.71	0.86	0.69
	30	0.67	0.76		
	60	0.60	0.62		
	90	0.57	0.57	1.17	0.98
Urine glucose	0	0.00	0.00	0.00	0.00
	30	0.00	0.00		
	60	0.00	0.00		
	90	0.00	0.00	0.00	0.00
Urine RBC	0	0.24	0.56	0.57	1.13
	30	0.37	0.76		
	60	0.33	0.84		
	90	0.23	0.63	0.17	0.41

Table 8: **Serum chemistry results for Groups P and C.**

		Group P		Group C	
Parameter	**Day**	**Mean**	**SD**	**Mean**	**SD**
ALT	0	51.91	35.25	68.75	48.06
	30	58.69	47.92		
	60	85.41	98.37		
	90	72.23	61.06	99.63	76.87
AST	0	53.63	22.08	54.00	18.98
	30	51.27	17.09		
	60	67.19	58.20		
	90	54.17	19.66	52.57	15.53
Bilirubin	0	14.61	14.20	24.00	20.97
	30	10.03	8.02		
	60	11.06	10.79		
	90	10.40	9.32	9.00	5.68
Bile acids	0	11.35	8.94	77.25	165.34
	30	14.10	9.44		
	60	11.03	9.99		
	90	25.32	33.05	18.48	11.41
Urea	0	5.40	1.43	5.10	1.44
	30	6.76	2.12		
	60	6.38	1.97		
	90	7.00	2.21	5.11	1.03
Creatinine	0	99.76	23.06	97.75	19.00
	30	107.13	23.23		
	60	111.38	25.20		
	90	111.90	23.50	91.25	16.10

Table 9: **Adverse events reported during the study.**

Adverse events	**Number of incidences**	**Number of dogs with a particular condition**
Diarrhoea	9	5
Vomition	6	3
Dark stool	4	2
Anorexia	3	2
Constipation	2	1
Weight loss	1	1
Urination	1	1
Increased water consumption	1	1

time, occult blood in faeces and gastric ulceration through gastroscopy were monitored[16]. The dogs were treated for 90 days and samples were taken on day 0, 7 30, 60 and 90[16]. GGT was increased in the control, etodolac and meloxicam and bleeding time increased in the meloxicam, ketoprofen and flunixin groups[16]. Clotting time was increased in the carprofen, flunixin, ketoprofen and meloxicam groups[16].Gastric ulceration was seen in the etodolac, ketoprofen and flunixin groups[16]. Carprofen and meloxicam induced the lowest frequency of gastrointestinal effects[16].

The long-term effects of carprofen were studied compared to placebo in a small group of medium to large dogs with a mean age of 5.7 ± 2.5 years over a period of 2 months[22]. Protein, albumin, urea, creatinine, ALP, AST and urinary protein creatinine ratio were studied at day 0, 30 and 60[22]. Serum albumin was lower in treated dogs[22]. No difference was found in serum and urine chemistry results[22].

In this study, pain scores as recorded by both veterinarians and owners showed statistical improvement from day 30 onwards. For the owner, some variables only became statistically significant after day 45. Statistical difference was also seen for the owners' pain evaluation between day 7 and days 60, 75 and 90. The veterinarians' evaluation of pain was also significantly different between days 30 and 90. These data suggest that a prolonged course of firocoxib may show continued improvement. This concept is supported by a dose-reduction study with meloxicam where differences where found to day 120[6,10], and in a study using tolfenamic acid in dogs following a femoral head excision, improved functionality was found in dogs treated for 4 months compared with normal post-operative treatment for 5 days[4]. This certainly poses the question as to what is an appropriate length of treatment for dogs with osteoarthritis. The data presented above would indicate that a longer course is better. More research is required to establish the optimum duration for dosing NSAIDs in dogs with osteoarthritis and the long-term effect on cartilage[2,3,7,19,23]. Does the increased production of proteoglycans translate into an improvement in the joints or does the disease process of osteoarthritis continue in spite of this benefit?

Bile acids were significantly raised in the treatment group between days 0 and 90, but the liver enzymes did not change during this study and correlated with the study in healthy dogs[25]. Bile acids are known to rise after food intake. Dogs were not controlled with regard to fasting and this may have resulted in the erratic high values seen in the study. It is important to realise that most of the results were not beyond the normal clinical range supplied by the laboratory. The changes seen may represent normal variation. Hepatoxicity has not yet been observed with firocoxib[8,24,25]. The control group had a higher mean value and a high standard deviation and had increased bile acids at day 0.

In veterinary medicine, carprofen has been documented to induce liver failure[17]. A number of NSAIDs have been withdrawn from the human market due to liver failure[1]. Most initial studies are underpowered to detect rare adverse events[1]. It has been suggested that a sample of 30 000 is required to detect these rare adverse events with a certainty of 95 %[1]. Sulindac, ibuprofen and diclofenac cause cholestatic liver injury[1]. NSAIDs have been shown to induce changes in bile salts that alter their conformation that makes them toxic to the gastrointestinal tract[20]. This change in conformation may affect bile flow and induce cholestatic liver damage. Does the rise in bile acids indicate cholestasis? The rise in bile acids and urea should be investigated further to exclude a possible rare underlying liver effect.

A rise in urea from the control group to the treatment group was detected on days 30 and 90. After 28 days treated with firocoxib in 6 dogs, a single dog developed a raised urea level but this also occurred during placebo treatment[25]. No gastric ulcers were detected in healthy dogs treated for 28 days with firocoxib[25]. A raised urea value in 12 of a 1000 dogs withdrawn from a firocoxib study has been reported[24]. An increase in urea (17.6 to 23.7 mg/dℓ) although not statistically significant, was shown in 128 client-owned dogs that received firocoxib[8]. These results did not exceed normal reference ranges.

A rise in urea can be related to renal dysfunction, a high protein diet or gastrointestinal bleeding. No increase in creatinine was observed in the treatment group over time and the urine analysis remained normal. This makes it unlikely that a decline in renal function increased the urea value. Gastric ulceration or gastrointestinal disease as a cause for the increase in urea can not be excluded. Gastrointestinal adverse events were seen and no specific tests were conducted to exclude gastrointestinal disease. Starving was not required for samples taken and this may have affected the results.

In 1000 dogs followed for 40 days that received firocoxib the most common adverse events associated with withdrawal from the study were: vomition 1.9 %, diarrhoea 0.6 % and vomition and diarrhoea 0.4 %[24]. In 128 dogs that received firocoxib for 30 days the most common adverse events were diarrhoea 0.8 %, vomition 3.9 %, anorexia 2.3 % and lethargy 0.8 %[8]. In total, 9.4 % of the dogs had an adverse event[8]. The most common adverse events seen in the present study were related to the gastrointestinal tract. The incidence seen in this study may represent the geriatric patient group that was targeted as opposed to the original and pre-marketing studies that sampled dogs between the ages of 7 months and 19 years, with the vast majority being middle-aged and relatively healthy individuals. These patients are potentially more likely to develop adverse events based on age-related deterioration in liver and renal function.

The result of this study may have been influenced by sample size. The sample size is relatively small; however, the results are still useful. This study shows that firocoxib is effective for managing pain associated with osteoarthritis and the improvement is seen up to day 90. The effect of NSAIDs in geriatric dogs has not been well researched and subtle changes reported here may represent part of normal aging. This should be borne in mind when interpreting these data. The drug is safe with minimal biochemical changes. The adverse events seen are in line with what has been reported previously. This is one of the 1st reports in geriatric veterinary patients and further follow-up and studies of other NSAIDs are required in this target population.

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