Approval Date: March 31, 2003

FREEDOM OF INFORMATION SUMMARY

NADA # 141-193

ZUBRIN™

Tepoxalin

Rapidly-Disintegrating Tablets

For Dogs

" for the control of pain and inflammation associated with osteoarthritis."

SCHERING-PLOUGH ANIMAL HEALTH
1095 Morris Ave.
P.O. Box 3182
Union, N.J. 07083-1982

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FREEDOM OF INFORMATION SUMMARY

1. GENERAL INFORMATION

NADA Number:	141-193
Sponsor:	Schering-Plough Animal Health Corporation 1095 Morris Ave. Union, N.J. 07083 Drug Labeler Code: 000061
Established Name:	tepoxalin
Proprietary Name:	ZUBRIN™ Rapidly-Disintegrating Tablets
Dosage Form:	Oral tablets: ZUBRIN™ is available as white, circular, freeze-dried, rapidly- disintegrating tablets which, when administered orally, disintegrate within seconds after placement in the mouth, thus allowing the contents to be swallowed.
How Supplied:	ZUBRIN™ Tablets are supplied in boxes containing 10 foil blisters each. Each foil blister contains 10 rapidly-disintegrating tablets of 30, 50, 100, or 200 mg tepoxalin.
How Dispensed:	Rx - Federal law restricts this drug to use by or on the order of a licensed veterinarian.
Amount of Active Ingredient:	Each rapidly- disintegrating tablet contains 30, 50, 100, or 200 mg tepoxalin.
Route of Administration:	Oral
Species/Class:	Dogs/Canine
Recommended Dosage:	Dosage: Administer 10 mg/kg (4.5 mg/lb) or 20 mg/kg (9.1 mg/lb) on the initial day of treatment, followed by a daily maintenance dose of 10 mg/kg. Due to observed variability in tepoxalin metabolism, a higher initial dose of 20 mg/kg may be given to increase the likelihood that plasma active metabolite levels will reach a minimum effective concentration following the first oral

administration. This could be beneficial to dogs that show signs of severe osteoarthritic pain. The duration of treatment at 10 mg/kg should be based on clinical response and patient tolerance of drug treatment.

Administration: Place the rapidly-disintegrating tablet into the dog's mouth. Keep the mouth closed for a sufficient amount of time (~4 seconds) to ensure tablet dispersion. ZUBRIN™ Tablets should be administered either with food or within 1 to 2 hours after feeding.

Due to tablet sizes, dogs weighing less than 3 kg (6.6 lbs) cannot be accurately dosed.

Pharmacological Category:	Non-steroidal Anti-inflammatory Drug
Indications:	ZUBRIN™ (tepoxalin) Tablets are indicated for the control of pain and inflammation associated with osteoarthritis in dogs.

2. EFFECTIVENESS:

a. Dosage Characterization:

(1) 10 mg/kg maintenance dose:

A multiple site field study (Study No. E99-473) was conducted in the United States to assess the dose response control of dogs with osteoarthritis when tepoxalin was administered using three different doses of ZUBRIN™ Tablets.

Fifty-two dogs with clinical signs attributable to osteoarthritis presented to veterinarians, and were randomly allocated to treatment with ZUBRIN™ at one of 3 doses (5.0 mg/kg, 7.5 mg/kg, and 10.0 mg/kg) for 7 consecutive days. Ease of ambulation, weight bearing, pain and resistance to palpation, pain and resistance to forced movement, and general attitude and demeanor were evaluated. The most effective dose among the three dose groups was 10 mg/kg. Sixteen dogs received 10 mg/kg tepoxalin on the initial day of therapy and for 6 additional consecutive days. Of these 16 dogs, 14 showed improvement in clinical signs related to osteoarthritis after 7 days of therapy at 10 mg/kg.

(2) 20 mg/kg initial day dose:

A study was conducted to determine the pharmacokinetic profile of tepoxalin administered orally to 12 dogs at an initial dose of 20 mg/kg, followed by a dose of 10 mg/kg once daily for six additional days (Study No. N00-576).

Results: Mean tepoxalin pharmacokinetic parameters in dogs (± standard deviation).

		T_{max} (hr)	C_{max} (ng/mL)	$T_{1/2}$ (hr)	AUC_{0-24}* (hr*ng/mL)
Tepoxalin	Day 0	2.3 ± 1.4**	780 ± 506	2.0 ± 1.2	3363 ± 1841
	Day 1	2.3 ± 1.9	529 ± 182	2.3 ± 1.4	2324 ± 1394
	Day 6	2.8 ± 4.2	637 ± 317	1.6 ± 0.6	2434 ± 1499
Active Metabolite	Day 0	4.7 ± 6.2	831 ± 357	13.7 ± 10.7	8460 ± 3527
	Day 1	2.7 ± 1.9	986 ± 323	12.4 ± 8.4	11297 ± 5728
	Day 6	6.8 ± 8.0	968 ± 486	13.4 ± 10.3	12094 ± 8195

* Where AUC represents the area under the concentration/time curve over either one complete dosing interval (active metabolite) or to the last quantifiable concentration (tepoxalin).
**standard deviation

Tepoxalin is rapidly absorbed after oral administration. Its half-life in plasma is short due to conversion to an active metabolite. The active metabolite has a long half-life which justifies once daily dosing of ZUBRIN™ Tablets. Clinical signs of toxicity, as demonstrated in safety studies, were dose related rather than related to the duration of dosing (see SAFETY section).

Substantial intrasubject and intersubject variability was associated with the pharmacokinetics of tepoxalin. As a result of these highly variable kinetics, it is recommended that when time to onset of pain relief is critical, therapy be initiated at a dose rate of 20 mg/kg to improve the likelihood that systemic drug concentrations rapidly and consistently exceed the minimum effective concentration of this compound and its active metabolite.

b. SUBSTANTIAL EVIDENCE (field study):

A controlled field study was conducted in dogs using the dosage of 20 mg/kg for one day, followed by 10 mg/kg daily for an additional 6 days. Tepoxalin was administered for one week to demonstrate the effectiveness and safety of tepoxalin tablets for the control of pain and inflammation associated with osteoarthritis.

ZUBRIN™ (tepoxalin) field study at small animal clinics in the US (Study No. 1930C-61-V98-372, Report No. 30116)

(1) Type of Study: Multi-Centered Controlled Field Study

(2) Investigators:

Investigator	Investigator
Andrew Pickering, DVM Wabash Valley Animal Hospital 3004 S. 7th Street Terre Haute, IN 47802	Todd Schadler, DVM Great Southern Animal Hospital 2685 South High Street Columbus, OH 43207
Roger Sifferman, DVM Bradford Park Veterinary Hospital 1255 East Independence Springfield, MI 65804	L. D. Eckermann, DVM Westbury Animal Hospital 4917 South Willow Drive Houston, TX 77035
K. S. Griffin, DVM W. Van Hooser, DVM Carriage Hills Animal Clinic 3200 Eastern Bypass Montgomery, AL 36116	Richard Benjamin, DVM Berkeley Dog & Cat Hospital 2126 Haste Street Berkeley, CA 94704
Robert Yelland, DVM Lewelling Veterinary Clinic 525 Lewelling Boulevard San Leandro, CA 94579	Donald Copeland, DVM Bellaire Richmond Animal Hospital 5808 Bissonnet Houston, TX 77081-6599
Jack W. Whitmore, DVM Stuebner Airline/Champions Veterinary Hospital 16116 Stuebner Airline Spring, TX 77379	Ben Garrett, DVM Garrett Veterinary Hospital 1846 South Oates Dothan, AL 36301

(3) General Design:

(a) Purpose: The objective of the study was to evaluate, under field conditions, the effectiveness and safety of ZUBRIN™ for the control of pain and inflammation associated with canine osteoarthritis.

(b) Animals: Two-hundred and five dogs were evaluated for safety and 122 (62 tepoxalin and 60 carprofen) were evaluated for effectiveness. The mean age of dogs was 8.1 years (4 months – 18 years).

(c) Control: The active control product was an approved carprofen tablet.

(d) Diagnosis: The diagnosis of osteoarthritis was based on medical history and physical examination, including radiography, and included cases of hip dysplasia, osteoarthritis and discospondylosis.

(e) Dosage Form: ZUBRIN™ (tepoxalin) rapidly-disintegrating tablet containing 50 or 200 mg of tepoxalin

(f) Route of Administration: Oral

(g) Dosages used:

Active control: 2.2 mg carprofen/kg twice daily for seven days.
Tepoxalin: 20 mg tepoxalin/kg on the first day followed by 10 mg/kg daily for six consecutive days.

(h) Test Duration: 7 days

(i) Parameters Measured on Day 0 and Day 6:

- Ease of ambulation/locomotion
- Weight bearing
- Pain and resistance to palpation
- Pain and resistance to forced movement
- General attitude
- An overall (general) evaluation was made on Day 6 by both the owner and the investigator. Animals were classified as "vastly improved", "improved", "no change" or "worse".

(4) Results: Results of the study showed statistically significant improvement for all parameters comparing Day 0 to Day 6 within the tepoxalin group.

Tepoxalin and Carprofen: Number Affected for Clinical Parameters of Osteoarthritis in Dogs

Parameter	**Ease of Ambulation & Locomotion**		**Weight Bearing**		**Pain & Resistance to Palpation**		**Pain & Resistance to Forced Movement**	
	T (n=62)	*C (n=60)*	*T (n=62)*	*C (n=60)*	*T (n=62)*	*C (n=60)*	*T (n=62)*	*C (n=60)*
Day 0								
Normal	1	2	6	6	4	5	0	2
Slight	18	20	23	26	20	14	19	13
Moderate	30	26	25	23	26	31	31	28
Severe	13	12	7	5	12	10	12	17
Day 6								
Normal	27	27	37	36	26	31	25	25
Slight	33	25	20	17	31	23	30	28
Moderate	3	7	5	6	5	5	7	6
Severe	0	1	0	1	0	1	0	1

T = Tepoxalin; C = Carprofen

Tepoxalin and Carprofen: Number Affected for General Attitude

General Attitude	Tepoxalin (n=62)		Carprofen (n=60))	
	Day 0	Day 6	Day 0	Day 6
% Normal	37	59	35	55
% Modified	25	3	25	5

Tepoxalin and Carprofen: Effectiveness for Investigator and Owner Evaluation

Parameter (Day 6)	Treatment Group	Vastly Improved (n)	Improved (n)	No Change (n)
Investigator Evaluation	Tepoxalin (n=62)	22	37	3
	Carprofen (n=60)	18	36	6
Owner Evaluation	Tepoxalin (n=62)	20	38	4
	Carprofen (n=60)	26	29	4

(5) Statistical analysis: After removing dogs that were normal on both days 0 and 6, scores for each endpoint were converted to a recording of "success" if the dog experienced a decrease of at least one score between day 0 and day 6, otherwise the dog was considered to have "failed" with respect to that endpoint. Ninety percent exact confidence intervals for the difference in the proportion of dogs scored as successes for each treatment were constructed. The lower bound of the confidence interval is taken as an estimate of the maximal negative difference in effectiveness for tepoxalin compared to the active control drug. Based on the estimated maximal differences, tepoxalin was considered noninferior to the comparator product. The success rates for the comparator product and the estimated maximal differences are displayed in the following table.

Estimated maximal differences between the success rates for tepoxalin and the comparator drug carprofen for each endpoint.

Clinical Endpoint	Percent Successes in Carprofen Comparator Group (x of n)	Percent Successes in Tepoxalin Group (x of n)	Lower Ninety Percent Confidence Bound
Ease of ambulation/locomotion	81% (47 of 58)	92% (56 of 61)	-2.5%
Weight Bearing	80% (43 of 54)	84% (46 of 55)	-11.4%
Pain on Palpation	87% (48 of 55)	86% (50 of 58)	-17.6%
Pain on Forced Movement	81% (48 of 59)	82% (51 of 62)	-13.1%
Investigator Evaluation	90% (54 of 60)	95% (59 of 62)	-6.6%
Owner Evaluation	92% (55 of 60)	94% (58 of 62)	-10.0%
General Attitude	80% (20 of 25)	88% (22 of 25)	-16.3%

(6) Conclusion: Under the conditions of this study, ZUBRIN™ Tablets administered orally at a dosage of 20 mg/kg once on the first day, followed by a dose of 10 mg/kg administered once daily for six consecutive days, were shown to be safe

and effective for the control of pain and inflammation associated with canine osteoarthritis.

(7) Adverse Reactions:
The following table lists the adverse reactions that were observed during the field study (dogs received either ZUBRIN™ Tablets or carprofen for 7 days):

Adverse reaction*	**Number of dogs treated with ZUBRIN™ Tablets** (n= 101)	**Number of dogs treated with carprofen** (n= 104)
Vomition	2	5
Diarrhea	4	0
Anorexia	0	1
Ineffectiveness	0	1
Incoordination	1	0
Death**	1	-

*Dogs may have experienced more than one of the observations during the study.
**Two days after the completion of the field study, one nine-year-old Labrador retriever became seriously ill and subsequently died. Necropsy results showed multiple gastric ulcerations (3-8 mm), anemia, and severe diffuse gastroenteritis. The dog's death could not be definitively attributed to the administration of tepoxalin.

3. TARGET ANIMAL SAFETY:

Two laboratory studies were conducted to evaluate the safety of tepoxalin when administered orally to dogs. A 26-week oral toxicity study (with an interim 13-week sacrifice) and a 1-year oral toxicity study provided safety data. In a third study, field safety was evaluated in 107 dogs receiving 28 consecutive days of ZUBRIN™ Tablet therapy in an uncontrolled field study.

The laboratory studies were conducted with drug substance suspended in hydroxypropylmethylcellulose and administered to dogs by gavage in split dosing (twice daily, given 4-5 hours apart) to maximize oral bioavailability. Bioavailability data was used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation.

a. Twenty-Six Week Oral Toxicity Study of Tepoxalin in Dogs (13-week interim report) (Study No. 21121:01:00, Report Numbers A-27657 & A-27658)

(1) Type of Study: 26-week oral toxicity study with a thirteen-week interim necropsy (The study was conducted in compliance with FDA's Good Laboratory Practices Regulations for Nonclinical Laboratory Studies (21 CFR Part 58).

(2) Study Director: Dr. E.V. Knight
The R.W. Johnson Pharmaceutical Research Institute
PRI Research Farm

(3) General Design:

(a) Purpose: To assess the toxicity of tepoxalin when administered orally to Beagle dogs for twenty-six weeks with a thirteen-week interim necropsy.

(b) Test Animals: Fifty-six Beagle dogs were assigned to four groups (7/sex/group). An interim sacrifice of 3 dogs/sex/group was conducted after 13 weeks of dosing. Animals were seven months of age at the time of initiation of dosing.

(c) Dosage Form: Tepoxalin micronized suspension at concentrations of 10 and 150 mg/mL (Bioavailability data was used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation.)

(d) Placebo Control: 0.5% Hydroxypropyl Methylcellulose Premium F4M

(e) Doses Used:

Doses Used in Study No. 21121:01:00/Report Numbers A-27658 and A-27657

Total Dose* (mg/kg/day)	Relative Dose**
0	0X
20	1-2X
100	10-20X
300	15-30X

*Total treatment dose was divided and administered twice daily.
**Relative dose refers to multiples of the recommended therapeutic dose of 20 mg/kg as a one-time induction dose, followed by a maintenance dose of 10 mg/kg.

(f) Route of Administration: Oral gavage

(g) Treatment Duration: Twenty-six weeks (with thirteen week interim sacrifice)

(h) Parameters Measured:

1 Clinical Observations
2 Physical Examination
3 Food Consumption
4 Body Weight

5 Mortality Check
6 Ophthalmoscopic Examination
7 Electrocardiographic Analysis
8 Hematology
9 Coagulation
10 Blood Chemistry
11 Urinalysis
12 Gross Pathology
13 Organ Weights
14 Histopathology

(4) Results:

13 week findings:

There were no drug-related changes in body weight gain, food consumption, clinical signs, or results of ophthalmologic examinations. Discolored feces ranging from white to yellowish tan were noted mainly in dogs receiving doses of 100 and 300 mg/kg/day. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract. No drug-related changes were observed in the clinical pathology parameters for the 20 and 100 mg/kg/day dosage groups. At weeks 6 and 14, one female dog in the 300 mg/kg/day group showed neutrophilic leukocytosis, decreased RBC, Hb and PCV, decreased serum total protein, decreased albumin, and decreased calcium (later confirmed to be a result of chronic gastric ulceration at the week 27 necropsy). The clinical pathology changes were attributed to the administration of tepoxalin. Two other females (20 mg and 100 mg groups) showed mild to moderate RBC, Hb and PCV decreases at week 14 that returned to predosage levels by week 27. These changes were considered possibly related to tepoxalin.

At 13 weeks, 6 dogs per treatment group were necropsied. Dogs in all dosage groups showed evidence of gastric irritation (mucosal hemorrhage and congestion) after 13 weeks: 1 in the 0 mg/kg dose group, 1 in the 20 mg/kg dose group, 3 in the 100 mg/kg group, and 2 dogs in the 300 mg/kg group. One of the 2 dogs that received the highest dose (300 mg/kg) showed gastric ulceration at the mid-study necropsy. The ulcers were confirmed histologically and attributed to the administration of tepoxalin.

26 week findings:

There were no drug-related changes in body weight gain, food consumption, clinical signs, or results of ophthalmologic examinations. Discolored feces ranging from white to yellowish tan were noted mainly in dogs receiving doses of 100 and 300 mg/kg/day. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract.

In the 20 mg/kg/day dosage group, one female dog showed RBC, Hb and PCV decreases at week 14 that returned to predosage levels by week 27. By the final week of the study, two female dogs in the 300 mg/kg/day dose group had decreased RBC, Hb, and PCV values; as well as increased WBC and neutrophil counts in one of these females at week 27

At 26 weeks, the remaining 8 dogs per group were necropsied. Necropsy results demonstrated gross gastric lesions in no dogs in the 0 mg/kg/day group, one dog in the 20 mg/kg/day group, two dogs in the 100 mg/kg/day group, and four dogs in the 300 mg/kg/day group. Gastric ulceration was confirmed by histopathology in the highest dose group (300 mg/kg/day) in 2 of the 4 dogs with gross gastrointestinal abnormalities. Dogs in the lower dose groups showed evidence of gastric irritation (mucosal hemorrhage and congestion) after 6 months treatment with tepoxalin.

(6) Conclusions:

Adverse reactions were dose related and resulted in gastric ulceration (with associated clinical pathology changes) in the high dose group (300 mg/kg/day). Abnormalities of the gastrointestinal tract (enteritis, mild mucosal hemorrhage and congestion) were noted in all dosage groups.

b. One-Year Oral Toxicity Study for Tepoxalin in Beagle Dogs (Study No. 92018, Report No. A-30023)

(1) Type of Study: One-year oral toxicity (The study was conducted in compliance with FDA's Good Laboratory Practices Regulations for Nonclinical Laboratory Studies, 21 CFR Part 58).

(2) Study Director:

Dr. E.V. Knight
The R.W. Johnson Pharmaceutical Research Institute
Route 202
Raritan, NJ

(3) General Design:

(a) Purpose: To assess the toxicity of tepoxalin when administered orally to Beagle dogs for fifty-two weeks

(b) Test Animals: Thirty-two Beagle dogs were assigned to four groups (4/sex/group). Animals were eight months of age at the time of initiation of dosing.

(c) Dosage Form: Tepoxalin micronized suspension at concentrations of 5, 15 and 50 mg/mL (Bioavailability data were used to establish comparability in drug exposure between the non-market gavage formulation and the final rapidly-disintegrating tablet formulation).

(d) Placebo Control: 0.5% Hydroxypropyl Methylcellulose Premium F4M

(e) Doses Used:

Doses Used in Study No. 92018/Report No. A-30023

Total Dose* (mg/kg/day)	Relative Dose**
0	0X
10	0.5-1X
30	1.5-3X
100	5-10X

*Total treatment dose was divided and administered twice daily.
**Relative dose refers to multiples of the recommended therapeutic dose of 20 mg/kg as a one-time induction dose, followed by a maintenance dose of 10 mg/kg.

(f) Route of Administration: Oral gavage

(g) Treatment Duration: Fifty-two weeks

(h) Parameters Measured:

1 Clinical Observations
2 Physical Examination
3 Food Consumption
4 Body Weight
5 Ophthalmoscopic Examination
6 Electrocardiographic Analysis
7 Hematology
8 Coagulation
9 Blood Chemistry
10 Urinalysis
11 Gross Pathology
12 Organ Weights
13 Histopathology

(4) Results:

Pale yellow to white material was frequently observed in the feces of tepoxalin treated dogs. The material was probably tepoxalin that was not absorbed from the gastrointestinal tract. Treatment related macroscopic

red and/or depressed foci were noted in the pyloric mucosa of the stomach of two female dogs in the 100 mg/kg/day dosage group. These changes were confirmed on histopathological evaluation as gastric erosion and ulceration. Gastric mucosal hemorrhage was noted in a third dog in this dosage group. No treatment-related microscopic changes were observed in the stomach of any dogs in the 10 or 30 mg/kg/day dosage groups.

Emesis occurred more frequently in the 100 mg/kg/day dogs:

Type of vomiting	**Dosage group**	**Number of dogs***
food vomiting	10 mg/kg/day	2
foamy vomiting	30 mg/kg/day 100 mg/kg/day	1 2
discolored vomiting	100 mg/kg/day	3
drug vomiting	100 mg/kg/day	1
mucoid vomiting	100 mg/kg/day	2

*Dogs listed may have vomited more than once

(6) Conclusions:

The study confirmed the occurrence of gastrointestinal abnormalities when tepoxalin is administered at exaggerated dosages. In the healthy dogs used in this study, an adequate safety margin existed for the oral treatment of dogs with tepoxalin at the recommended maintenance dose of 10 mg/kg/day.

c. ZUBRIN™ (tepoxalin) European field study 439: **Safety of ZUBRIN™ tablets, administered orally for 28 days, for the control of pain and inflammation associated with osteoarthritis in dogs**

(1) Study Dates: June to December, 1999

(2) Investigators:

Investigator	**Address**
Dr. H. Maltot	Clinique Veterinaire de Senlis 12-14 Place des Arenes, 60300 Senlis – France
Dr. L. Kern	Clinique Veterinaire 4 rue Meissonier, 75017 Paris – France
Dr. F. Miguet	Clinique Veterinaire de Fleurie Place de l'Eglise, 69820 Fleurie – France
Drs. Schwarz & Winzinger	Georgenstrasse 22b D-82152 Planegg – Germany
Dr. Kendlinger	Moltkestrasse 2 D-84453 Mühldorf – Germany

(3) Study Design: An open (uncontrolled, unmasked) study with a total of 107 dogs enrolled at 5 sites.

(4) Purpose of Study: The study demonstrates the field safety of tepoxalin rapidly-disintegrating tablets (market formulation) administered orally for 28 days for the control of pain and inflammation associated with osteoarthritis (OA) in dogs.

(5) Description of test animals: A total of 107 dogs were enrolled in this study by 5 investigators (9 to 29 dogs per clinic). All 107 enrolled dogs were used in the safety evaluation.

(6) Control group: none

(7) Treatment group: Tepoxalin rapidly-disintegrating tablets (market formulation) were administered to all dogs included in the study.

(8) Inclusion criteria: Dogs of various breeds, ages, sex and weights exhibiting pain and/or inflammation from an arthritic condition were candidates for this field study.

(9) Exclusion criteria: Pregnant dogs or dogs specifically destined for reproduction were not enrolled in this study. Dogs which had received analgesic, antipyretic or antiinflammatory drugs (corticosteroids, NSAIDs) within the previous 5 days were excluded from this study. Post-surgical cases were excluded from this study.

(10) Owner consent: Consent of the owner was obtained before any dog was included in the study.

(11) Dosage form: Tepoxalin's market formulation is a white, circular, freeze-dried, fast-dissolving tablet that disintegrates in approximately four seconds after placement in the mouth. The test article consisted of 3 different sizes of ZUBRIN™ Tablets containing 50, 100 or 200 mg of tepoxalin.

(12) Drug dosage, frequency, duration and route of administration: The tepoxalin dosage was 20 mg/kg orally on day 0, followed by 10 mg/kg from day 0-27.

(13) Relationship to feeding: within an hour after feeding

(14) Study parameters:

Physical examination: On Day 0, a medical history of the case was taken, including an evaluation of the general physical condition, a description of

significant findings which may impact overall health or progression of the healing process, and a list of concurrent treatments. Osteoarthritis was confirmed by radiography. The dogs returned to the clinic on Day 13 and again after completion of the treatment period.

Clinical pathology: On Day 0, Day 13 and Day 27, a blood sample was drawn for CBC. Blood chemistry profiles (ALT, AST, GGT, ALP, TP, CK, albumin, urea, creatinine, Ca, P, Na, K, Cl) were established on Day 0 and Day 27.

Adverse reactions: The dogs were also observed daily by the owner for adverse reactions.

(15) Results:

Demographics:

Dogs of 34 different breeds or mixed breeds were represented in this study. The following table shows that, in general, older dogs tended to enroll for the control of OA pain:

Site number	Mean age (years)	Minimum age (years)	Maximum age (years)
1	9.8	2	13.3
2	9.2	2.5	14
3	10.7	2.9	15
4	10.2	3	17.3
5	9.3	1.2	17.3

Clinical Pathology:

Hematology parameters were measured pretreatment, at Day 13 and Day 27. The proportion of dogs with a "normal" PCV fell below 80% (77.2%) at the second visit and went back up over 80% at the last visit. Only 2 cases with low PCV at the interim visit exhibited diarrhea and/or vomiting at some point during the study.

Serum chemistry parameters were measured pretreatment, at Day 13 and Day 27. One dog showed elevated ALT at the last visit (>200 IU/L). Three dogs had highly elevated BUN (>100 mg/dL) associated with increased creatinine. One case had highly elevated BUN and creatinine on Day 0 (pretreatment: 231 mg/dL and 3.4 mg/dL, respectively) and Day 6 (3 days after treatment termination: 143 mg/dl and 3.6 mg/dL, respectively). Another case had highly elevated BUN and creatinine on Day 0 (pretreatment: 165 mg/dL and 3.2 mg/dL, respectively) and at the end of the study (post treatment termination: 182 mg/dL and 3.4 mg/dL, respectively). These were also associated with low PCV, RBC, and hemoglobin. A third case had highly elevated BUN (>100 mg/dL) and slightly elevated

creatinine on Day 0; post treatment biochemistry results were not available for this dog.

Adverse Reactions:

Of the 107 dogs enrolled and used in the safety analysis, 97 (90.7%) completed the 28 day course of therapy. Of the 10 dogs that discontinued therapy before the completion of the study, 7 were related to adverse events (see below). The most commonly reported adverse reaction was gastrointestinal (GI) upset which was manifested by at least one of the following: diarrhea, vomiting, loss of appetite, soft feces, and enteritis. Other adverse reactions which may be related to GI upset include: fatigue/lethargy, flatulence, and eating grass.

Adverse reactions observed in dogs that participated in an uncontrolled field study treated with ZUBRIN™ Tablets for 28 days

Adverse Reaction	**Number of Dogs* (n= 107)**	**Median Number of Days Observed (Range)**
diarrhea	23	2 days (1 to 31)
vomiting	21	1 day (1 to 8)
anorexia/inappetance	9	3 days (1 to 15)
enteritis	4	3 days (1 to 5)
lethargy	3	3 days (2 to 15)
flatulence	1	31 days
trembling	1	27 days
increase appetite	1	2 days
eating grass	1	3 days
incontinence	1	3 days
hair loss	1	5 days
death	1**	-

*dogs may have experienced more than one of the observations during the study.
**described in detail below. This table does not include a dog that died following surgery for splenic torsion (described below)".

Eight dogs exhibited both vomiting and diarrhea, but only five dogs exhibited both signs simultaneously.

Hematology results indicated that detectable blood loss occurred in three of the cases that were reported with diarrhea or vomiting. Two of the three cases had slightly lower PCV values than the lower laboratory normal limit, prior to treatment (Day 0) and posttreatment (Day 6 and Day 31, respectively; PCV ranging from 34.5 to 37.1%). Both of these dogs also had highly elevated BUN and creatinine at both time points suggesting an underlying chronic renal failure that could be the cause of the observed anemia. The third dog also had slightly lower PCV values than the lower laboratory normal limit the day before he died (see description below).

In seven cases (6.5%), the adverse events were severe enough to warrant discontinuation of therapy. One of these seven cases was removed from the study by the owner after the dog vomited on Day 0. In 5 of these 7 cases, discontinuation of therapy resulted in resolution of the adverse event. In 2 cases, death ensued after termination of therapy. These cases are described in detail below:

- The first case was an 8.5 year old spayed German Shepherd weighing 38 kg. She vomited after the first dose was administered on Day 0. Vomiting was noted on subsequent days. By Day 4, the vomiting was described as repetitive and the investigator decided to terminate treatment and initiated symptomatic treatment (GI protectants and an antiemetic). Three days after termination of therapy, the dog presented with continuous vomiting and a diagnosis of splenic torsion was made. A splenectomy was performed that day at 7:30 pm. The dog recovered from anesthesia at 9:30 pm. Death occurred the following morning at approximately 5:00 am. Necropsy revealed an acute peritonitis caused by perforation of the duodenum. All other organs appeared normal. While the cause of death was definitively due to a splenic torsion, the investigator was unsure whether the splenic torsion initiated the dog's vomiting, or the vomiting initiated the splenic torsion.

- The second case was a 12 year old male German Shepherd weighing 38 kg. He received tepoxalin from Day 0 to Day 12. Diarrhea was reported from Day 3 to Day 12, vomiting on Day 8 and Day 11, and loss of appetite on Day 9. On Day 13, at the planned interim visit, the dog was scored as Greatly Improved by both the owner and investigator. Despite the clinical improvement, the investigator and owner decided to remove the dog from the study due to the diarrhea which was described as becoming darker. At the time of this interim assessment, the dog had a PCV of 35.5%, which was lower that its day 0 PCV of 52.3%. Despite evidence of GI bleeding, the dog was given 4 mg of dexamethasone IM. A spasmolytic agent (benzadamide) was also administered IM. The dog died the following night. No necropsy results were available for this dog.

  This dog's initial bloodwork showed a white blood cell count (16.4 WBC/nL) with band neutrophils (2%). The dog had elevated liver enzymes (ALT = 122 U/L; SAP = 643 U/L). On day 13, the leukogram had worsened (WBC = 27.7/nL; band neutrophils = 11%).

  Note: Lack of adherence to standard precautionary NSAID warnings contributed to the deaths of the two dogs in this study, including preexisting clinical abnormalities, inappropriate continuation of the use of tepoxalin in the face of GI abnormalities and concurrent use of corticosteroids.

  Conclusions: The most commonly reported adverse reactions were related to GI abnormalities (diarrhea, vomiting, inappetance, soft feces, enteritis, death).

4. HUMAN SAFETY:

This drug is intended for use in dogs, which are non-food animals. Because this new animal drug is not intended for use in food-producing animals, data on human safety pertaining to drug residues in food were not required for approval of this NADA.

Human Warnings are provided on the product label as follows: "Keep out of reach of children. Not for human use. Consult a physician in cases of accidental human exposure."

5. AGENCY CONCLUSIONS:

The data in support of this NADA comply with the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act and 21 CFR Part 514 of the implementing regulations. The data demonstrate that ZUBRIN™ Tablets (tepoxalin), when used under labeled conditions of use in dogs, is safe and effective.

ZUBRIN™ Tablets are restricted to use by or on the order of a licensed veterinarian because professional expertise is needed to diagnose canine osteoarthritis and to monitor response to treatment.

Under section 512(c)(2)(F)(i) of the Federal Food, Drug, and Cosmetic Act, this approval qualifies for FIVE years of marketing exclusivity beginning on the date of the approval because no active ingredient of the new animal drug has previously been approved.

PATENT INFORMATION:

U. S. Patent No. 5,164,381 - Expires: November 17, 2009
U. S. Patent No. 4,826,868 - Expires: May 29, 2006

6. APPROVED LABELING:

A. Package Insert
B. Blister Foil
C. Box Label
D. Client Information Sheet