Date of Approval: January 20, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-547

Zorbium™

buprenorphine transdermal solution

Cats

Zorbium™ is indicated for the control of postoperative pain associated with surgical procedures in cats

Sponsored by:

Elanco US Inc.

Executive Summary

Zorbium™ (buprenorphine transdermal solution) is approved for the control of postoperative pain associated with surgical procedures in cats. Buprenorphine is an opioid analgesic with a high binding affinity for various subclasses of opiate receptors, particularly mu, in the central nervous system. The mu opiate receptor is responsible for pain relief, and buprenorphine works by changing the way the central nervous system responds to pain.

In *in vitro* systems, buprenorphine is classified as a partial mu agonist, which means it doesn't bind as strongly to the receptor as full agonists, such as morphine. Buprenorphine slowly dissociates from the mu receptor, resulting in prolonged analgesia.

Zorbium™ should only be administered in a veterinary hospital by veterinarians or veterinary technicians who are trained in the handling of potent opioids. The drug should be applied topically to the top of the cat's neck at the base of the skull 1 to 2 hours before surgery. It should not be applied if the skin is diseased or injured. The dose volume of Zorbium™ is either 0.4 mL (8 mg) for cats weighing from 1.2 kg to 3 kg or 1 mL (20 mg) for cats weighing > 3 kg to 7.5 kg, which is a dose range of 2.7 to 6.7 mg/kg.

Zorbium™ is rapidly absorbed and sequestered into the skin. It provides analgesia within 1 to 2 hours following administration and continually releases buprenorphine from the skin into the systemic circulation over a period of days. A single application provides analgesia for 4 days.

Proprietary Name	Established Name	Application Type and Number	Sponsor
Zorbium™	buprenorphine transdermal solution	New Animal Drug Application (NADA) 141-547	Elanco US Inc.

Safety and Effectiveness

The sponsor conducted a field study in client-owned cats to evaluate the effectiveness of Zorbium™ to control pain after an elective surgery of a spay or neuter and concurrent forelimb declaw. Enrolled cats were of various breeds (75% were domestic shorthair) and between 4 months and 5 years of age. Most cats did not have pre-existing conditions or medications, and over half were female. The cats received either Zorbium™ or a vehicle control (a solution without buprenorphine) 1 to 2 hours before surgery. All cats in both the treatment and control groups received an intramuscular injection of dexmedetomidine hydrochloride as a preanesthetic and had a metacarpal ring block with lidocaine after induction of anesthesia.

Each cat was assessed for pain before surgery and at multiple timepoints post-operatively, starting from the time the cat was first in sternal recumbency (considered anesthetic recovery) to 96 hours (4 days) after sternal recumbency. The assessor first observed the cat from a distance for sedation and dysphoria (agitation). If the cat displayed no signs of sedation or dysphoria, then the assessor performed an interactive pain assessment that evaluated the cat's 1) behavior from a distance; 2) behavior after social interaction; and 3) pain on palpation. Based on these observations, the assessor determined if the cat's pain control was adequate or

inadequate. If the cat's pain was inadequately controlled, it was administered another pain medication and considered a treatment failure. More cats in the treatment group were determined to have adequate pain control for 4 days following surgery compared to the control group.

The adverse reactions observed from the time of anesthetic induction until the cats were in sternal recumbency after surgery included hypothermia, hypotension, hypertension, tachycardia, and sedation. These reactions were seen in both the treatment and control groups and are commonly seen in cats after general anesthesia and surgery.

Hyperthermia was the only adverse reaction observed in more than 10% of cats treated with Zorbium™ after the day of surgery (from 24 to 96 hours after surgery). The percentage of treated cats with hyperthermia decreased over time, from 66.4% on Day 0, to 28.3% on Day 1, to 6.2% on Day 4.

The sponsor also conducted three laboratory safety studies in young, healthy cats:

1. A margin of safety study - Zorbium™ was administered topically every 4 days for a total of 3 doses at 0X, 1X, 2X, and 3X the highest labeled dose of 6.7 mg/kg per cat.

2. An acute margin of safety study - Zorbium™ was administered topically once at 0X, 0.5X, 1.5X, and 4.5X the highest labeled dose of 6.7 mg/kg per cat.

3. A cardiovascular safety study - Zorbium™ was administered topically every 4 days for a total of 3 doses at 0X and 1X the highest labeled dose of 6.7 mg/kg per cat.

In all three studies, Zorbium™ caused dose-independent euphoria (exaggerated social and playful behavior), dysphoria (agitation and restlessness), mydriasis, hyperthermia, and constipation. There were no clinically significant effects on body weight, heart rate, electrocardiogram (ECG), respiratory rate, serum chemistry, hematology, urinalysis, gross pathology, or histopathology results.

User Safety
Because Zorbium™ is applied topically, people can potentially be exposed to the drug by touching the area on the cat's neck before the skin completely dries or by touching residual buprenorphine remaining on the cat's skin before all the drug is absorbed. Therefore, the sponsor conducted two human user safety studies to evaluate this exposure risk to people:

1. A drying time study concluded that dose volumes of 1.2 mL or less of the transdermal solution (without buprenorphine) applied to the top of the cat's neck at the base of the skull dried completely within 30 minutes following administration.

2. A human user risk assessment concluded that following complete drying of the solution (30 minutes), there is no health risk to adults or children associated with exposure to residual buprenorphine in the home environment. The risk to veterinary professionals from direct exposure when handling the

drug or a treated cat from the time of application to complete drying is reduced by following the instructions on the drug's labeling.

Zorbium™ is a DEA Schedule III controlled substance with an abuse potential similar to other Schedule III opioids. The drug can also cause serious, life-threatening adverse reactions in people, such as respiratory depression and depression of the central nervous system. Like all approved opioids, the labeling for Zorbium™ includes a black box warning with important human safety warnings. The labeling also includes detailed information regarding the safety to people who handle, administer, or are exposed to the drug and additional information about drug misuse, abuse, addiction, and criminal diversion.

Conclusions

Based on the data submitted by the sponsor for the approval of Zorbium™, FDA determined that the drug is safe and effective when used according to the labeling.

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I. GENERAL INFORMATION

A. File Number

NADA 141-547

B. Sponsor

Elanco US Inc.
2500 Innovation Way
Greenfield, IN 46140

Drug Labeler Code: 058198

C. Proprietary Name

Zorbium™

D. Drug Product Established Name

Buprenorphine transdermal solution

E. Pharmacological Category

Opioid analgesic, DEA Schedule III (CIII) controlled substance

F. Dosage Form

Transdermal solution

G. Amount of Active Ingredient

20 mg/mL

H. How Supplied

Applicator tubes that deliver a dose volume of either 0.4 mL or 1 mL (20 mg/mL buprenorphine) in multi-packs of 10 tubes.

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

This product should only be administered by veterinary personnel.

Zorbium™ is for administration only once for the surgical procedure. Zorbium™ should be applied 1 to 2 hours before surgery. A single application provides analgesia for 4 days. Zorbium™ should only be applied topically to the dorsal cervical area at the base of the skull. Do not apply if dorsal cervical skin is diseased or injured. The dosage of Zorbium™ is 1.2 – 3.1 mg/lb (2.7 – 6.7 mg/kg) administered topically as the entire tube contents according to the following dosing table:

Pounds of Body Weight	Kilograms of Body Weight	Dose of Zorbium™
2.6 to 6.6	1.2 to 3	0.4 mL (8 mg) pink tube
> 6.6 to 16.5	> 3 to 7.5	1 mL (20 mg) green tube

K. Route of Administration

Topical

L. Species/Class

Cats

M. Indication

Zorbium™ is indicated for the control of postoperative pain associated with surgical procedures in cats.

II. EFFECTIVENESS

The effectiveness of Zorbium™ (buprenorphine transdermal solution) for the control of postoperative pain associated with surgical procedures in cats was demonstrated in a field effectiveness study in client-owned cats (Study No. NCY05-C-21).

A. Dosage Characterization

Laboratory Dose Selection Studies

A laboratory pharmacokinetic (PK) study was conducted in 12 cats (4 per group) administered 10, 30, or 50 mg of transdermal buprenorphine. Results indicated that the rate of elimination of buprenorphine transdermal solution is faster than its rate of absorption from the skin (flip-flop kinetics) and the absorption determines the terminal half-life. The mean terminal half-life ranged between 78.3 and 91.2 hours. Doses greater than 30 mg/cat appeared to result in less than proportional increases in plasma buprenorphine concentrations.

Three separate thermal threshold (TT) antinociceptive studies were conducted using a cross-over study design in cats administered buprenorphine transdermal solution, a placebo control, or an active control (0.02 mg/kg intramuscular

buprenorphine). The studies demonstrated that buprenorphine transdermal solution doses between 10 and 50 mg/cat had peak effects similar to 0.02 mg/kg intramuscular (IM) buprenorphine, with a duration of action of at least 2 to 3 days. These studies also indicated that at the 10 mg/cat dose, the onset of antinociceptive action was 2 to 4 hours, while doses of 20 mg/cat and higher had an onset of action of 1 to 2 hours.

An integrative pharmacokinetic/pharmacodynamic (PK/PD) analysis of these 4 laboratory studies described above indicated that for larger cats, transdermal buprenorphine doses above 20 mg/cat resulted in diminished increases in the antinociceptive effect, and that the 20 mg/cat dose was most likely to provide the optimal product onset of antinociceptive action (2 hours) and duration of action (4 days).

Based on the laboratory studies, 2 transdermal buprenorphine doses of 4 mg and 8 mg were selected for smaller cats (1.2 to 3 kg) and 2 transdermal buprenorphine doses of 10 mg and 20 mg were selected for larger cats (> 3 to 7.5 kg) for further evaluation in a pilot field study.

Pilot Field Study

A multicenter, prospective, randomized, masked, vehicle-controlled pilot field study to evaluate buprenorphine transdermal solution was conducted in 106 client-owned healthy cats undergoing elective surgical reproductive sterilization (castration/ovariohysterectomy), in conjunction with forelimb onychectomy (declaw). Cats were randomly assigned to 1 of 3 treatment groups: transdermal vehicle solution, low dose (4 or 10 mg/cat) buprenorphine transdermal solution, or high dose (8 or 20 mg/cat) buprenorphine transdermal solution administered once topically to the dorsal cervical region. Pain assessments and adequacy of pain control were measured through 4 days. Rescue analgesic was administered if pain control was inadequate. The primary variable was treatment success or failure for adequate pain control. A cat was considered a treatment success if it had adequate pain control without needing rescue analgesia. A cat that was removed from the study due to an adverse event was considered a treatment failure. The high dose (8 or 20 mg per cat) provided a greater proportion of treatment success without an increase in adverse events. Based on the results of the study, the doses of 8 mg (for cats weighing 3 kg or less) and 20 mg (for cats weighing greater than 3 kg) per cat were chosen for administration during the clinical field study to confirm the effectiveness of Zorbium™ for the control of postoperative pain associated with surgical procedures in cats.

B. Substantial Evidence

Title: Placebo-controlled Field Safety and Effectiveness of Zorbium™ (buprenorphine transdermal solution) for the Control of Postoperative Pain Associated with Surgical Reproductive Sterilization Performed in Conjunction with Forelimb Onychectomy in Cats. (Study No. NCY05-C-21)

Study Dates: April 2013 to March 2014

Study Locations: Twelve veterinary clinics from the following locations participated in this study.

Burnsville, MN
Farragut, TN
Fort Collins, CO
Franklin, IN
Gainesville, FL
Hickory, NC
Indianapolis, IN
Littleton, CO
Ocala, FL (2 separate clinics participated)
Springfield, MO
Seminole, FL

Study Design: This was a multicenter, prospective, masked, randomized, vehicle-controlled field study.

Objective: To evaluate the field safety and effectiveness of Zorbium™ for the control of postoperative pain associated with surgical procedures.

Study Animals: The study enrolled 228 client-owned cats presented for elective reproductive sterilization and forelimb onychectomy. The cats were various breeds (75% were domestic shorthair), 4 months to 5 years old, weighing 1.1 - 5.7 kg (2.5 – 12.5 lb) with 53.9% being female and 46.1% male. The majority of cats enrolled did not have pre-existing conditions or receive concurrent medications. The most common pre-existing conditions and medications involved parasitic infections or treatments and routine vaccines. Cats were hospitalized for the entire 96-hour study.

Experimental Design: The cats were randomized to receive Zorbium™ or a vehicle control at a 1:1 ratio (113 in the Zorbium™ group and 109 in the vehicle control group). Cats were dosed once prior to intubation. The effectiveness analysis included 219 evaluable cats (112 in the Zorbium™ group; 107 in the vehicle control group). The study was conducted in accordance with Good Clinical Practice guidelines.

Table II.1. Treatment Groups

Treatment Group	Dose	Number of Cats
Zorbium™	2.7-6.7 mg/kg	113
Vehicle control [a]	0 mg/kg	109

[a]The control was the topical solution without buprenorphine (vehicle control of 50 mg/mL padimate O in ethanol).

Inclusion: The study included cats of any breed, 4 months of age or older, and reproductively intact; with no clinically relevant medical abnormality detected on screening hematology, serum chemistry, or physical examination; with a score of P1 (normal healthy patient) or P2 (mild systemic disease) as defined by the American Society of Anesthesiologists (ASA); and signed owner consent.

Exclusion: A cat was excluded if it did not meet the inclusion criteria above; was extremely fractious; was pregnant, lactating, or intended for breeding; had received a prohibited medication (a non-steroidal anti-inflammatory drug or glycosaminoglycan within 24 hours prior to dosing, a short-acting corticosteroid within 14 days of dosing, or a long-acting corticosteroid within 30 days prior to dosing (Day 0); was injured or had diseased skin at the dosing site; had a known sensitivity to opioids, amide-type local anesthetics, or any of the allowed anesthetic agents; or had a history of blood dyscrasia, hepatic, renal, or cardiac disease, seizures, or any other concurrent medical condition that would preclude the cat from the study.

Drug Administration: The dose was administered once, topically to the dorsal cervical area of the cat, 1 - 2 hours prior to intubation. The dose was determined based on the weight of the cat (see Table II.2). To administer the solution, the tip of the tube was placed directly on the skin surface by parting the fur. The cat was restrained for approximately 2 minutes to allow drying, and contact with the application site was avoided for 30 minutes.

Table II.2 Dose as Determined by Weight

Treatment Group	Weight of Cat	Dose (Volume)	Number of Cats
Zorbium™	1.2 to 3 kg (2.6-6.6 lbs)	8 mg (0.4 mL)	61
	>3 to 7.5 kg (>6.6 to 16.5 lbs)	20 mg (1 mL)	52
Vehicle control	1.2 to 3 kg (2.6-6.6 lbs)	0 mg (0.4 mL)	65
	>3 to 7.5 kg (>6.6 to 16.5 lbs)	0 mg (1 mL)	44

Anesthesia and Surgery: Anesthetic protocols were similar across all clinics. All cats were fasted overnight. All cats, regardless of treatment group assignment, received a single intramuscular injection of dexmedetomidine hydrochloride (5 µg/kg) as a preanesthetic 30 minutes prior to induction. A 4-point metacarpal ring block was performed with lidocaine after induction. The anesthetic regimens were similar across all clinics. Cats were anesthetized with a combination of induction agents (propofol, ketamine, diazepam, midazolam, or zolazepam) and then either isoflurane or sevoflurane for anesthetic maintenance administered "to effect." Reproductive sterilization and onychectomy were performed concurrently on all study animals. Supplemental heat or subcutaneous fluids were administered as necessary.

Measurements and Observations: Physical examination including body weight, and sample collection for hematology and serum chemistry analysis, were performed at screening and at study end. Body weight was obtained on Day 0 to determine the dose administered and obtained again at 24, 48, 72, and 96 hours after sternal recumbency after surgery. Safety was monitored during the study

through clinical observations and monitoring of physiological parameters. Physiological parameters for indirect mean arterial blood pressure (MAP), oxygen hemoglobin saturation, end tidal carbon dioxide, heart rate, respiratory rate, body temperature, and ECG were assessed every 10 minutes during surgery. Physiological parameters for MAP, heart rate, respiratory rate, temperature, thorax auscultation, urination, defecation, and appetite were assessed postoperatively (after sternal recumbency) at approximately 0 and 30 minutes, and at 1, 2, 4, 8, 12, 24, 28, 48, 72, and 96 hours. Values outside the defined reference ranges were documented as adverse events. The times of the various stages of recovery (vaporizer shut off, extubation, head lift, and sternal recumbency) were recorded and the overall recovery from anesthesia was scored as excellent, acceptable, or unacceptable. A trained assessor evaluated the cats postoperatively for sedation, dysphoria, and pain prior to surgery, and postoperatively, at 0, 15, 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 12, 24, 28, 32, 48, 52, 56, 72, 76, 80, and 96 hours following sternal recumbency. Although there were scheduled evaluation timepoints, pain intervention medication could be administered any time during the study if an animal demonstrated the need for additional pain control.

The absence or presence of sedation and dysphoria were evaluated first by observing the cat from a distance. If both sedation and dysphoria were absent, then scores for behavior were determined as part of an interactive pain assessment with the following observations:

1. Behavior From a Distance
   The unattended cat was quietly observed in its cage at a relatively unobtrusive distance (approximately 10 feet). The cat was observed for general appearance, behavior, and body tension.

   Scores:
   0=Comfortable: content and quiet, comfortable when resting; interested in or curious about surroundings; ambulates normally; minimal body tension
   1=Uncomfortable: may appear/exhibit: slightly unsettled; less interested in surroundings; hair coat appears rough or fluffed up; may constantly groom an area that is painful or irritating; ambulates with noticeable weight shifting behavior but still places affected limbs on floor; mild to moderate body tension
   2=Distressed: may appear/exhibit: constantly yowling, growling, or hissing; may bite or chew at wound; unlikely to move, prostrate; unaware of surroundings; barely or unable to ambulate, significant weight shifts or non-bearing behavior; moderate to severe body tension

2. Behavior Following Social Interaction:
   For social interaction, the cat's cage was approached, the cage door was then opened, and the cat was stroked. The resulting behavior, including body tension, was observed.

   Scores:
   0=Normal: content and quiet, interested in or curious in the assessor as he/she approaches; does not object to stroking; minimal body tension

1=Mildly Abnormal: content or slightly unsettled; less interested in assessor's approach, but will look around to see what is going on; slight reduction in level of social behavior but does not overtly object to stroking; mild body tension
2=Moderately Abnormal: decreased responsiveness to assessor's approach, seeks solitude; quiet, tolerates attention, may even perk up when stroked, as long as painful area is avoided; mild to moderate body tension
3=Severely Abnormal: refuses to be stroked and may display aggression without provocation; growls or hisses at non-painful stroking; unlikely to move, prostrate; unaware of surroundings; may be rigid to avoid painful movement; moderate to severe body tension

3. Pain on Palpation
The soft tissue adjacent to the reproductive surgical site was gently palpated

Scores:
0=Minimal: may react to palpation of surgical site, but at a pressure level nearly equivalent to what could be applied in a cat that had not undergone surgery
1=Moderate: reacts to palpation of surgical site at a pressure level less than what could be applied in a cat that had not undergone surgery, response to moderate palpation may be aggressive, including growling or hissing, and/or cat may try to escape upon palpation
2=Severe: growls or hisses at non-painful palpation or any level of physical contact to surgical area; reacts aggressively to non-painful palpation, adamantly pulls away to avoid any contact; alternatively, may be rigid to avoid painful movement

After all the observations and assessments were made (as described above), the observer assessed if pain control was adequate or inadequate. No specific score (cumulative or taken from any individual section) was definitively associated with the need for rescue analgesia. Cats whose pain was inadequately controlled were administered rescue pain medication and considered a treatment failure.

Statistical Methods: The experimental unit was the individual cat. The primary effectiveness variable was treatment outcome (success or failure) for each cat included in the effectiveness analysis. Treatment success was defined as a cat that did not require rescue analgesia, need opioid reversal, or experience an adverse event suspected to be related to treatment through the entire 96-hour post-recovery period. Cats removed from the study due to inadequate pain control, opioid reversal, or an adverse event suspected to be treatment-related were treatment failures. A generalized linear mixed model (GLMM) with binomial distribution and a logit link function was fitted to compare the proportions of treatment success between treatment groups. The model included treatment as a fixed effect and site and site-by-treatment interaction as random effects. Estimated success rates and confidence intervals were back-transformed from the GLMM least squares estimates. Zorbium™ was to be considered effective if the estimated success rate was greater in the Zorbium™ group than in the vehicle control group and the hypothesis testing was significant at 2-sided $\alpha = 0.05$.

Results: The primary effectiveness variable was evaluated for 219 cats (112 Zorbium™ and 107 vehicle control cats). Comparison of the Zorbium™ group and the vehicle control group over the 96-hour post-recovery period demonstrated a statistically significant difference in the treatment success rate (p = 0.0003).

Table II.3. Primary Effectiveness Variable Evaluation

Treatment Group	Number of Cats With Treatment Success/Total in Treatment Group	Success rate (%; back-transformed least squares means[a])	95% Confidence Interval (back-transformed)	p-value
Zorbium™	89/112	81	0.70-0.89	0.0003
Vehicle control	42/107	40	0.28-0.53	n/a

[a]Least squares means are based on an analysis using a generalized linear mixed model (GLMM) including treatment as a fixed effect and site and the site-by-treatment interaction as random effects.

A total of 23 Zorbium™ and 65 vehicle control cats were removed from the study due to inadequate pain control or adverse reactions. Of these, 19 and 63 were removed due to inadequate pain control, respectively. Most of these treatment failures occurred on the day of surgery in both groups; however, there were 4 Zorbium™ cats and 5 vehicle control cats removed due to inadequate pain control between 1 and 3 days after surgery.

Intraoperatively: Zorbium™ administration had little, if any, effect on intraoperative physiological variables, and there was no statistically significant difference between Zorbium™ and vehicle control for any of the variables with the exception of end tidal carbon dioxide. The slight increase in mean end tidal carbon dioxide (2.47 mmHg) in the Zorbium™ group compared to the control group was not considered clinically significant. Hypothermia was common in both groups during surgery and supplemental heat was provided to 82% of cats during surgery.

Postoperatively: The overall mean postoperative body temperature was significantly different and numerically higher (p-value = 0.0004) in the Zorbium™ group than in the vehicle control group. Mean postoperative body temperatures in the Zorbium™ group were slightly above the normal range at 4 and 8 hours postoperatively (mean ± SD of 102.7 ± 1.2°F and 102.6 ± 1.0°F, respectively [normal range: 100.5 - 102.5°F]). Mean indirect arterial blood pressures (MAP) were similar between the two treatment groups over time. Urination, defecation, appetite, and daily body weights after surgery were not affected by Zorbium™. Fifteen cats in the Zorbium™ group had an increased fibrinogen at discharge, compared to 2 cats in the vehicle control group.

Adverse Reactions: Safety was evaluated in a total of 222 cats with 113 cats in the Zorbium™ group and 109 cats in the vehicle control group. There were no deaths during the study. No cats received an opioid reversal agent. Three Zorbium™ and 2 vehicle control group cats were removed from the study due to hyperthermia suspected to be treatment-related. One cat in the Zorbium™ group was removed due to fractious behavior 30 minutes following surgery.

Adverse reactions were defined as any single excursion outside the normal range [normal ranges for body temperature, blood pressure, heart rate, and respiratory rate: 100.5 - 102.5°F body temperature; 60 - 120 mmHg mean arterial pressure; 88 - 180 beats per minute for heart rate; and 24 - 44 breaths per minute for respiratory rate]. The following tables summarize the reported adverse reactions.

Table II.4. Adverse Reactions from Anesthetic Induction through Sternal Recumbency

Adverse Reaction‡	Zorbium™ (N = 113)	Vehicle Control (N = 109)
Hypothermia	37 (32.7%)	29 (26.6%)
Hypotension	31 (27.4%)	28 (25.7%)
Hypertension	27 (23.9%)	18 (16.5%)
Tachycardia	14 (12.4%)	14 (12.8%)
Sedation	12 (10.6%)	7 (6.4%)
Oxygen saturation ≤ 90%	6 (5.3%)	2 (1.8%)
Bradycardia	4 (3.5%)	2 (1.8%)
Hyperthermia	3 (2.7%)	4 (3.7%)

‡Physiological adverse reactions were defined as any single excursion outside the normal range at any 10 minute interval during the entire duration of anesthesia.

After the cat was sternal (anesthetic recovery), observations and assessments were recorded for 96 hours. The following adverse reactions were reported.

Table II.5. Adverse Reactions After Anesthetic Recovery (Sternal Recumbency)

Adverse Reaction‡	Zorbium™ (N = 113)	Vehicle Control (N = 109)
Hypothermia	107 (94.7%)	105 (96.3%)
Hyperthermia	84 (74.3%)	62 (56.9%)
Sedation	64 (56.6%)	48 (44.0%)
Tachypnea	56 (49.6%)	70 (64.2%)
Hypotension	50 (44.2%)	51 (46.8%)
Hypertension	42 (37.2%)	34 (31.2%)
Bradycardia	34 (30.1%)	45 (41.3%)
Tachycardia	32 (28.3%)	39 (35.8%)
Anorexia	25 (22.1%)	32 (29.4%)
Dysphoria	20 (17.7%)	29 (26.6%)
Diarrhea	11 (9.7%)	11 (10.1%)

Adverse Reaction‡	Zorbium™ (N = 113)	Vehicle Control (N = 109)
Bradypnea	11 (9.7%)	7 (6.4%)
Leukocytosis	6 (5.3%)	4 (3.7%)
Hyperactivity	2 (1.8%)	9 (8.3%)

‡Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 4 days postoperatively.

Hyperthermia was the only adverse event observed in more than 10% of cats in the Zorbium™ group after the day of surgery (24 - 96 hours). The percentage of cats in the Zorbium™ group with hyperthermia decreased over time from 66.4% on Day 0 to 28.3% on Day 1, and to 6.2% by Day 4. A summary of adverse reactions (from anesthetic recovery through 96 hours after recovery) in cats in the Zorbium™ group by study day is reported in Table II.6.

Table II.6. Adverse Reactions in Zorbium™ Cats (N = 113) by Day:

Adverse Reaction‡	Day 0	Day 1	Day 2	Day 3	Day 4
Hypothermia	106 (93.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)	2 (1.8%)
Hyperthermia	75 (66.4%)	32 (28.3%)	18 (15.9%)	14 (12.4%)	7 (6.2%)
Sedation	64 (56.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Tachypnea	51 (45.1%)	5 (4.4%)	2 (1.8%)	3 (2.7%)	4 (3.5%)
Hypotension	42 (37.2%)	2 (1.8%)	1 (0.9%)	4 (3.5%)	2 (1.8%)
Hypertension	28 (24.8%)	2 (1.8%)	1 (0.9%)	1 (0.9%)	1 (0.9%)
Anorexia	25 (22.1%)	3 (2.7%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Bradycardia	24 (21.2%)	3 (2.7%)	2 (1.8%)	3 (2.7%)	5 (4.4%)
Tachycardia	24 (21.2%)	4 (3.5%)	0 (0.0%)	1 (0.9%)	1 (0.9%)
Dysphoria	20 (17.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Bradypnea	8 (7.1%)	2 (1.8%)	0 (0.0%)	0 (0.0%)	1 (0.9%)
Hyperactivity	1 (0.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.9%)

‡Physiological adverse reactions were defined as any single excursion outside the normal range following anesthetic recovery (sternal recumbency) through 96 hours postoperatively.

Conclusion: Zorbium™ at a dose of 2.7 - 6.7 mg/kg applied once topically 1 to 2 hours prior to intubation is effective and has an adequate safety profile for the control of postoperative pain associated with surgical procedures in cats.

III. TARGET ANIMAL SAFETY

The safety of Zorbium™ administered to cats for control of postoperative pain associated with surgical procedures is supported by three laboratory studies performed in healthy cats. The administration of Zorbium™ resulted in dose independent euphoria, dysphoria, mydriasis, increased body temperature, and constipation. There were no clinically significant effects on body weight, heart rate, ECGs, respiratory rate, serum chemistry, hematology, urinalysis, gross pathology, or histopathology results.

A. Margin of Safety Laboratory Study

Title: Target Animal Safety Study of a 1X, 2X, or 3X Dose of Transdermal Buprenorphine Solution Administered every Four Days for Three Doses in Four-Month-Old Cats. (Study No. NCY05-L-18)

Study Dates: June 2013 to July 2013

Study Location: Rockwood, TN

Study Design:

Objective: The objective of this study was to evaluate the safety of Zorbium™ administered topically every 4 days for 3 doses at 0X, 1X, 2X, and 3X the highest clinical dose of 6.7 mg/kg per cat.

Study Animals: The study included 32 intact domestic short-haired cats (16 males, 16 females), approximately 4 months old and weighing 1.7 - 2.3 kg at Day -1, determined to be healthy based on physical examination and clinical pathology. Cats were individually housed during the study.

Experimental Design: Cats were stratified by gender, and within gender cats were randomized to treatment. The day of necropsy (Day 12 or 13) was also designated on the Randomization Record so that equal numbers of animals of each gender and treatment group would be necropsied on each scheduled day. The study was a masked laboratory study conducted in accordance with the Good Laboratory Practice (GLP) regulations.

Drug Administration: Cats were administered either Zorbium™ at a dose of 6.7 mg/kg (1X), 13.3 mg/kg (2X), or 20 mg/kg (3X) or vehicle control at a volume equivalent to the 20 mg/kg (3X) Zorbium™ group. The solution was administered topically every 4 days directly to the skin surface on the dorsal cervical region by parting the fur.

Table III.1. Treatment Groups in Target Animal Safety Study for Cats Administered Zorbium™ (20 mg/mL solution):

Dosage Group	Dose (mg/kg/day)	Number of Cats (Males/Females)	Zorbium™ Administration
0X	0 mg/kg	4M, 4F	Once on Day 0, 4, and 8
1X	6.7 mg/kg	4M, 4F	Once on Day 0, 4, and 8
2X	13.3 mg/kg	4M, 4F	Once on Day 0, 4, and 8
3X	20 mg/kg	4M, 4F	Once on Day 0, 4, and 8

Measurements and Observations: The cats were evaluated twice a day for health observations, including eliminations and assessment of dose site. Food consumption was measured once daily. Samples for hematology and serum chemistry analysis were collected prior to dosing on Day -1, prior to dosing on Days 4 and 8, and on Day 12 or 13. To facilitate blood sample collection, the cats were administered dexmedetomidine hydrochloride intramuscularly, and then administered atipamezole intramuscularly after sample collection was complete (except for Day 12/13). Urine samples for urinalysis were collected prior to dosing and on Day 12 or 13. Physical examination was performed prior to dosing on Day -1 (pre-treatment); Days 0, 4, and 8 at 2 hours (± 30 min) post-dosing; Day 8 prior to dosing; and Day 12 or 13. Body weight was measured prior to dosing on Day -1, Day 2 at 2 hours post-dosing, Day 8 prior to dosing, and Day 12 or 13. Clinical observations (dysphoria and mydriasis) and physiological variables (mucous membrane color, capillary refill time, rectal body temperature, heart rate, and respiratory rate) were measured prior to each dose administration and at 1, 2, 4, 8, 12, 24, 36, 48, and 72 hours after dose administration and prior to necropsy. At the conclusion of the study, cats were euthanized and necropsied for pathology and histopathology.

Dysphoria was scored as follows:
0: normal
1: sedated with the cat subdued and less responsive to human interaction with sleeping, tail curling, or purring
2: euphoric exaggerated social and playful behavior with meowing, rolling, kneading with forepaws, play-biting, or rubbing head or body on cage
3: mildly dysphoric with a state of uneasiness and discord with absent staring, hyper-responsiveness, swaying, vocalization, or possible increased locomotor activity with no overt signs of fear or disorientation or aggression but could initially appear sedated and then startle suddenly
4: dysphoric with a state of anxiety or agitation with staring, hyper-responsiveness, sudden movements, vocalization, fearful or aggressive, or increased locomotor activity with obvious disorientation

Statistical Methods: For the continuous variables measured at more than one time point after each dose, a repeated measures analysis of covariance model was performed, including the fixed effects of dose group, sex, time and all the 2 and 3 way interactions within each dosing period, where animal was identified as the subject in the repeated statement. Baseline measurements were included in

the model as covariates. For continuous variables measured once, an analysis of variance model was performed, including the fixed effects of dose group, sex and the 2 way interaction. For gender specific continuous variables measured once, an analysis of variance model was performed, including a fixed effect of dose group. Except for the 3-way interaction term which was tested at $\alpha = 0.05$, all other hypothesis testing were conducted at $\alpha = 0.10$.

Results:

All cats survived to study termination.

Clinical Observations and Examinations: Application sites were visually normal in all cats at all times. Application site pruritus was noted on Day 4 at 2 hours after dosing in all groups, including vehicle control.

Two hours after dosing on Day 4, 9 cats (3 in the 0X group, 2 in the 1X group, 3 in the 2X group, and 1 in the 3X group) were tachypneic. After dosing on Day 8, only one of these cats (in the 0X group) was tachypneic. Respiratory rates in all groups were above the reference range during the entire study, but this finding was not clinically relevant.

Cats administered Zorbium™ had higher body temperatures compared to the 0X group throughout the study. Increased body temperature primarily occurred during the first 8 hours after the first dose and was observed in the majority of cats administered buprenorphine. Elevated temperatures ranged from 102.6°F to 104.5°F. The highest temperatures occurred at 2 hours after the first dose, gradually decreasing by 24 hours. By 3 days after dose administration, body temperatures in cats administered Zorbium™ had returned to levels observed in the vehicle control group. After the second and third doses (Days 4 and 8), mean temperatures in all Zorbium™ groups were again higher than in the vehicle control group, but not higher than the normal reference range.

Constipation occurred in the majority of the study cats, including 0X group cats. Among all treatment groups, 20 cats had at least 3 consecutive observations (1.5 days) of "no feces." Three cats (2 in the 1X group and 1 in the 3X group) were examined and treated for constipation with a laxative. For all other cats with recordings of "no feces," the absence of feces resolved without treatment. Diarrhea was observed in 2 of the 0X group cats (Day 1 and Day 11).

All cats administered Zorbium™ had mydriasis 8 hours after the first dose administration and half of these cats still had mydriasis at 24 hours after dose administration. Mydriasis completely resolved between 48 - 72 hours after dose administration. Four cats (1 in the vehicle control group, 2 in the 1X group, and 1 in the 3X group) had conjunctivitis at the examinations prior to necropsy.

Sedation after each dose administration was noted in all groups, including vehicle control, and resolved by 48 hours after each dose administration. Two hours after the first dose there were abnormal behaviors (hyperactivity in 6 cats, agitation in 5 cats, anxiety in 1 cat) noted in cats administered Zorbium™. One cat in the 3X group was anxious and aggressive prior to a dose administration. During the first 4 hours after the first dose, dysphoria was more prevalent in the Zorbium™ groups, was not dose dependent, and mean scores were similar among all 3

Zorbium™ groups (score of ≤ 2). Maximum dysphoria scores in the Zorbium™ groups reached 3 (mildly dysphoric) between 1 - 2 hours after the first dose; on the other 2 dosing days (Days 4 and 8), maximum scores were 2 (euphoric).

Body weight, mucous membrane color, and heart rate were unaffected by buprenorphine administration (similar values among all treatment groups, including vehicle control).

Food Consumption: Food consumption was similar in all groups, including vehicle control. There was no emesis observed in any cat during the study.

Clinical Pathology: Alanine aminotransferase values (reference range 27 - 93 U/L) were elevated in two cats: 197 U/L for a 0X male on Day 4 and 119 U/L for a 3X male on Day 4 (normal 93 U/L). There were no clinically relevant findings for other clinical pathology variables, including quantitative or qualitative urinalysis variables.

Organ Pathology/Histopathology: No gross lesions were noted in any cats in any dose group. At the application site, minimal to mild lymphoplasmacytic infiltration of the dermis and/or hair follicles was noted in all groups, including vehicle control cats.

Conclusions: This study demonstrated that buprenorphine transdermal solution has an adequate margin of safety for the control of postoperative pain associated with surgical procedures when administered at up to 6.7 mg/kg. Administration of Zorbium™ or vehicle control resulted in pruritus at the application site in all groups after the first dose, constipation, and increased lymphocytes and plasma cells at the application site on histopathology. Zorbium™ administration resulted in elevated body temperature, mydriasis, dysphoria, and abnormal behaviors (hyperactivity, agitation, anxiety, and aggression), when compared to vehicle control.

B. Acute Tolerance Safety Study

Title: Pilot Study: Acute Margin of Safety Study of Transdermal Buprenorphine Solution in Cats following a Single Dose Administration. (Study No. NCY05-X-17).

Type of Study: Pilot laboratory study

Study Dates: May 2012 to August 2012

Study Location: Rockwood, TN

Study Design:

Objective: To evaluate the acute margin of safety of buprenorphine transdermal solution in cats following a single dose administration.

Study Animals: The study included 24 domestic short-haired cats (4 intact males, 4 neutered males, and 16 intact females), 1 - 3 years old and weighing 2.2 - 5.8 kg at first dose administration.

Experimental Design: The study cats were randomly assigned to one of four treatment groups. Randomization was blocked by body weight. The study was a masked laboratory study conducted in accordance with the GLP regulations.

Table III.2. Treatment Groups in Acute Tolerance Safety Study

Treatment Group	Buprenorphine Dosage	Transdermal Solution Concentration	Transdermal Solution Volume	Number of Cats and Gender
0X	0 mg/kg	0 mg/mL	0.3 mL/kg	6 (2 M/4 F)
0.5X	3.3 mg/kg	12.5 mg/mL	0.3 mL/kg	6 (2 M/4 F)
1.5X	10 mg/kg	25 mg/mL	0.4 mL/kg	6 (2 M/4 F)
4.5X	30 mg/kg	25 mg/mL	1.2 mL/kg	6 (2 M/4 F)

Drug Administration: Cats were administered either Zorbium™ at 3.3 mg/kg (0.5X), 10 mg/kg (1.5X), or 30 mg/kg (4.5X), or vehicle control (50 mg/mL padimate O in ethanol). The solution was administered topically one time directly to the skin surface of the dorsal cervical region by parting the fur.

Measurements and Observations: Complete physical examinations, body weight, and sample collection for hematology and serum chemistry analysis were performed on all cats on Day -1, 3, and 7. Clinical observations of dysphoria, mydriasis, rectal body temperature, and heart rate were assessed/measured on Day 0 before dosing and at 2, 4, 8, and 12 hours following dose administration. Assessments were repeated on Days 1, 2, 3, 4, and 7 (24, 48, 72, 96, and 168 hours (± 1 hr) post-dosing, respectively). Abnormal animal health observations (vomit, urine, feces, diarrhea) were conducted twice daily throughout the study (Day -1 through Day 7); other abnormal animal health observations were also documented.

Dysphoria was scored as follows:
0: normal
1: sedated with the cat subdued and less responsive to human interaction with sleeping, tail curling, or purring
2: euphoric exaggerated social and playful behavior with meowing, rolling, kneading with forepaws, play-biting, or rubbing head or body on cage
3: was mildly dysphoric with a state of uneasiness and discord with absent staring, hyper-responsiveness, swaying, vocalization, or possible increased locomotor activity with no overt signs of fear or disorientation or aggression but could initially appear sedated and then startle suddenly
4: dysphoric with a state of anxiety or agitation with staring, hyper-responsiveness, sudden movements, vocalization, fearful or aggressive, or increased locomotor activity with obvious disorientation

Results: All cats survived to study termination. Cats administered Zorbium™ had similar dysphoria scores and displayed euphoric behavior (dysphoria score = 2) within 4 hours of dose administration. One cat (0.5X) scored 3 (mildly dysphoric) at 3 timepoints and 4 (dysphoric) at 1 timepoint, between 4 - 24 hours post-

dose. Five other cats had a score of 3 (mildly dysphoric) during the study. All vehicle control cats were considered normal (dysphoria score = 0) throughout the study except for one cat at one timepoint (96 hours, score = 2).

Almost all cats administered Zorbium™ had mydriasis noted from 2 to 48 hours after dose administration and none of the vehicle control cats had mydriasis during the study.

Elevated body temperature (> 102.5°F) was recorded for one control cat, four cats in 0.5X group, three cats in 1.5X group, and four cats in the 4.5X group at one or more timepoints after dose administration.

Tachycardia (> 240 beats per minute) occurred in two cats in the 0.5X group and two cats in the 4.5X group at one or more timepoints after dose administration.

Three cats (one cat in the 1.5X group on Day 1; two cats in the 4.5X group on Day 6) were administered one dose of laxative for constipation after observations of abdominal distension, irregular bowel movement, and/or hard/dry feces. Two cats (one cat in the 0.5X group and one cat in the 4.5X group) were observed to have abdominal distension.

Body weight was unaffected by Zorbium™ administration in the 0X, 0.5X, and 1.5X groups. Body weight decreased for all but one cat in the 4.5X group with a maximum weight loss of 0.3 kg from Day -1 to Day 7 during the study for 2 cats.

Serum sodium values were increased after dose administration for one cat administered vehicle control and eight cats administered Zorbium™.

Serum chloride values were increased after dose administration for three cats administered Zorbium™.

Conclusions: This study demonstrated an acceptable margin of safety for Zorbium™ for the control of postoperative pain associated with surgical procedures in cats. Administration of buprenorphine transdermal solution resulted in dysphoria, mydriasis, elevated body temperature, tachycardia, constipation, decreased body weight, and increased sodium and chloride, when compared to vehicle control.

C. Cardiovascular Safety Study

Title: Target Animal Cardiovascular Safety of a 1X Dose of Transdermal Buprenorphine Solution Administered Every Four Days for Three Doses in Cats. (Study No. NCY05-L-20).

Type of Study: Laboratory study

Study Dates: April 2013 to February 2014

Study Location: Mattawan, MI

Study Design:

Objective: To evaluate the cardiovascular safety of Zorbium™, administered topically every four days at doses equivalent to 0X and 1X the maximum labeled dose of 6.7 mg/kg for three doses, in conscious, freely-moving cats.

Study Animals: The study included 8 domestic short-haired cats (4 male, 4 female), 5.5 to 8 months old and weighing 3.15 - 4.5 kg at Day -1. The cats were acclimated for 49 days prior to surgical implantation of a telemetry device for continuous monitoring of body temperature, direct arterial blood pressure, and ECG. Following the surgical implantation, the cats recovered for at least 10 days prior to first dose administration.

Experimental Design: The cats were randomly assigned within gender to either the 0X (vehicle control) or 1X (buprenorphine transdermal solution) group. The study was a masked laboratory study conducted in accordance with the GLP regulations.

Drug Administration: Cats were administered either Zorbium™ at 6.7 mg/kg (1X) or vehicle control (0X, 50 mg/mL padimate O in ethanol) on Days 0, 4, and 8. The transdermal solution was administered topically, directly to the skin surface of the dorsal cervical region, by parting the fur.

Measurements and Observations: Body temperature, direct arterial blood pressure (systolic, diastolic, and mean arterial), heart rate, and ECG (QRS duration, RR, PR, QT, and QT intervals) were remotely continuously monitored from 2 hours prior to the first dose administration through 4 days following the last administration (Day 12). Telemetry-measured variables were collected and summarized in 1 minute time intervals and reported in 60 minute time bins. Body weight was measured the day before each dose administration. Cageside animal health observations were performed at least twice daily and detailed clinical examinations were conducted during each dosing interval.

Statistical Methods: The data were tabulated as the arithmetic mean, with standard deviation (SD), median, minimum, and maximum for each variable, treatment, and gender. A repeated measures mixed effects analysis of covariance was conducted on all the continuously measured variables reported in 60 minute time bins. Evaluation of this study was based on descriptive statistics.

Results: All cats survived to study termination. Blood pressure values were variable by time over the course of recording periods in both groups. Direct blood pressure (systolic, diastolic, and mean arterial) was clinically unaffected in the cats administered the 1X dose for 3 doses.

Buprenorphine caused increases in temperature compared to baseline or the control group, although body temperatures fluctuated in both groups. In the control group, the maximum temperature recorded was 102.6°F; it was recorded at 93 hours after the first dose. In the 1X group, the maximum temperature recorded was 103.4°F; it was recorded at 20 hours after the first dose.

Heart rates were variable by time over the course of recording periods in both groups. However, Zorbium™ increased the mean heart rate from 164.3 to 179.5 beats/minute. The magnitude of the increase was small (15.2 beats/minute); therefore, the observed increase was not considered clinically significant.

Increased heart rate was most obvious during the first and second dose periods; after the third dose, the differences between mean heart rate were smaller. All cats had sinus rhythm or sinus arrhythmia, both of which are normal rhythms in cats. One cat had an intraventricular conduction disturbance on all ECGs. This conduction disturbance was present prior to administration of Zorbium™ and was not test article related. All other ECGs were qualitatively within normal limits.

There were no clinically significant effects of treatment group on ECG intervals. RR, PR, QT, and to a lesser degree, QRS interval durations are influenced by heart rate; therefore, variations in these parameters over time were expected. A sporadic statistical decrease in PR interval and increase in QRS interval over time did not follow any clear relationship to Zorbium™ administration. The differences in PR interval and QRS duration were considered to be related to the observed diurnal variations in heart rate over time. No clinical abnormalities were observed during the study.

Conclusions: This study demonstrated an adequate safety profile, regarding cardiovascular parameters, for Zorbium™ for the control of postoperative pain associated with surgical procedures in cats.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

A. Human User Safety Studies

Drying Time: A study was conducted in 20 cats randomized to 1 of 5 treatment groups (4 cats per group). Each group was evaluated at a different post-dosing time point (5, 15, 30, 45, or 60 minutes). All cats received a single 1.2 mL application of vehicle transdermal solution to the dorsal cervical region. The application site was blotted once with a tissue (Kimwipes®) at the respective treatment group time point. The tissue was removed immediately after blotting and visually inspected to determine if it was wet or dry. All tissues were wet at 5 minutes. At 15 minutes post-application, 1 of 4 tissues were dry. At 30, 45, and 60 minutes, all tissues were dry. The study conclusion was that vehicle transdermal solution dose volumes of 1.2 mL or less applied to the dorsal cervical region of cats dried completely within 30 minutes following administration.

Residual Buprenorphine: Zorbium™ delivers a dose volume of 0.4 mL (8 mg buprenorphine) or 1 mL (20 mg buprenorphine). A study was conducted in cats to determine the amount of residual buprenorphine that can be wiped off with a cotton glove at the application site following a single administration of 10 or 20 mg buprenorphine transdermal solution. Twenty-four (24) adult domestic shorthaired cats were randomized to 1 of 6 treatment groups (4 cats per group). Groups 1, 2, and 3 were administered a 10 mg dose (0.62 mL) and wiped post-dosing at different time points (2, 24, and 96 hours, respectively). Groups 4, 5, and 6 were administered a 20 mg dose (1.0 mL) and wiped at the corresponding

post-dosing time points (2, 24, and 96 hours, respectively). A different cotton glove was used for each time point.

Gloves were assayed for buprenorphine. The lower limit of quantitation (LLOQ) of the method was 1 µg/glove. Buprenorphine was not measurable on any of the pre-dosing (Day -1) cotton glove samples. For the 10 mg dose, the mean residual buprenorphine amounts gradually decreased over time following dosing from 76.2 µg /glove (0.76% of the applied dose) at 2 hours post-dosing to 23.4 µg /glove (0.23%) at 96 hours post-dosing. For the 20 mg dose, the amounts decreased from 137 µg /glove (0.69%) at 2 hours post-dosing to 83.0 µg/glove (0.42%) at 96 hours post-dosing. The estimated residual buprenorphine half-life was 84.3 (90% CI: [47.5 - 377]) hours.

A human user risk assessment of buprenorphine transdermal solution was conducted. Topical residual buprenorphine of 137 µg at 2 hours following administration of 20 mg buprenorphine transdermal solution was used for the user risk assessment as the worst case of residual amount available for human exposure. User safety risk characterization by calculation of the Margin of Exposure (MOE) for adults and children by the dermal route, and for children by direct and indirect oral route of exposure, were all greater than 10 (> 10 = 'no appreciable risk'). Following complete drying of the solution (30 minutes), there is no appreciable health risk to adults or children associated with residual buprenorphine exposure in the home environment (Table V.1).

Table V.1: Risk Characterization of Topical Residual Buprenorphine Exposure in Human Users by Route, Age, and Margin of Exposure (MOE)

Route	Age	MOE	Risk*
Dermal	Adult	146	None
Dermal	Pediatric	31	None
Direct Oral	Pediatric	15	None
Indirect Oral	Pediatric	94	None

*MOE > 10 considered to have no health risk

The risk to medical professionals from direct exposure when handling transdermal buprenorphine solution between product application and complete drying (30 minutes after application) is mitigated by warning statements and instructions on the product label and by wearing gloves, protective glasses, and a laboratory coat.

B. User Safety Labeling

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Zorbium™, and regarding abuse potential:

HUMAN SAFETY WARNING

Abuse Potential
ZORBIUM contains buprenorphine, an opioid that exposes humans to risks of misuse, abuse, and addiction, which can lead to overdose and death. Use of buprenorphine may lead to physical dependence. The risk of abuse by humans should be considered when storing, administering, and disposing of ZORBIUM. Persons at increased risk for opioid abuse include those with a personal or family history of substance abuse (including drugs or alcohol) or mental illness (e.g. depression).

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with accidental exposure to or with misuse or abuse of ZORBIUM. Monitor for respiratory depression if human exposure to buprenorphine occurs. Misuse or abuse of buprenorphine by swallowing, snorting, or injecting poses a significant risk of overdose and death.

Accidental Exposure
Because of the potential for adverse reactions associated with accidental exposure, ZORBIUM should only be administered by veterinarians or veterinary technicians who are trained in the handling of potent opioids. Accidental exposure to even one tube of ZORBIUM, especially in children, can results in fatal overdose of buprenorphine.

Risks From Concurrent Misuse or Abuse with Benzodiazepines or Other CNS Depressants
Concurrent misuse or abuse of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death.

See Human Safety for detailed information.

HUMAN SAFETY WARNINGS:
Not for use in humans. Keep this and all medications out of reach of children and pets.

Human User Safety While Handling* ZORBIUM *in the Hospital:

Protective Covering: Do not come into direct contact with ZORBIUM. Wear impermeable latex or nitrile gloves, protective glasses, and a laboratory coat when applying ZORBIUM.

Mucous Membrane or Eye Contact During Application:
Direct contact of ZORBIUM with the eyes, oral, or other mucous membranes could result in absorption of buprenorphine and the potential for adverse

reactions. If accidental eye, oral, or other mucous membrane contact is made during application, flush the area with water and contact a physician immediately. If wearing contact lenses, flush the eye first and then remove the contact lens.

Skin Contact During Application: Following application to the cat, allow a minimum drying time of 30 minutes before direct contact with the application site. If human skin is accidentally exposed to ZORBIUM, wash the exposed area immediately with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions.

Drug Abuse, Addiction, and Diversion of Opioids:
Controlled Substance:
ZORBIUM contains buprenorphine, a Schedule III controlled substance with an abuse potential similar to other Schedule III opioids.

Abuse:
ZORBIUM contains buprenorphine, an opioid substance, that can be abused and is subject to misuse, abuse, and addiction, which may lead to overdose and death. This risk is increased with concurrent use of alcohol and other central nervous system depressants, including other opioids and benzodiazepines.

ZORBIUM should be handled appropriately to minimize the risk of diversion, including restriction of access, the use of accounting procedures, and proper disposal methods, as appropriate to the clinical setting and as required by law.

Prescription drug abuse is the intentional, non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects. Buprenorphine has been diverted for non-medical use into illicit channels of distribution. All people handling opioids require careful monitoring for signs of abuse.

Storage and Disposal:
ZORBIUM is a Schedule III opioid. Store in a locked cabinet according to federal and state controlled substance requirements/guidelines. Any unused or expired tubes must be destroyed by a reverse distributor; for further information, contact your local DEA field office or call Elanco US Inc. at 1-888-545-5973.

Information for Physician: ZORBIUM transdermal solution contains a mu opioid partial agonist (20 mg buprenorphine/mL). In the case of an emergency, provide the physician with this package insert. Naloxone may not be effective in reversing respiratory depression produced by buprenorphine. The onset of naloxone effect may be delayed by 30 minutes or more. Doxapram hydrochloride has also been used as a respiratory stimulant.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Zorbium™, when used according to the label, is safe and effective for the control of postoperative pain associated with surgical procedures in cats.

A. Marketing Status

This product is restricted to use by or on the order of a licensed veterinarian because it is a DEA Schedule Class III opioid with a potential for human abuse. Furthermore, professional expertise is needed to provide guidance for the control of postoperative pain. The veterinarian also monitors patients for possible adverse effects of the drug.

B. Exclusivity

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

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.