Date of Approval: November 9, 2017

FREEDOM OF INFORMATION SUMMARY

SUPPLEMENTAL NEW ANIMAL DRUG APPLICATION

NADA 106-111

Telazol®

tiletamine and zolazepam for injection

Dogs

The effect of the supplement is for intravenous administration in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

Sponsored by:

Zoetis Inc.

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I. GENERAL INFORMATION

A. File Number

NADA 106-111

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Telazol®

D. Product Established Name

Tiletamine and zolazepam for injection

E. Drug Enforcement Agency (DEA) Schedule

Telazol® (tiletamine and zolazepam for injection) is a nonnarcotic, nonbarbiturate dissociative and minor tranquilizing anesthetic and is a Class III controlled substance.

F. Pharmacological Category

Anesthetic, DEA Schedule class III controlled substance

G. Dosage Form

Injectable Solution

H. Amount of Active Ingredient

100 mg/mL total. 50 mg/mL tiletamine and 50 mg/mL zolazepam.

I. How Supplied

10 mL glass, sterile, multi-dose vials

J. Dispensing Status

Rx

K. Dosage Regimen

Intravenous (IV) For Induction of Anesthesia Followed by Maintenance with an Inhalant Anesthetic:
In dogs, for induction of anesthesia, administer TELAZOL intravenously at 1-2 mg/lb (2.2-4.4 mg/kg) body weight to effect. TELAZOL should be administered slowly, over 30-45 seconds; after approximately 30-60 seconds, the dog's level of

consciousness, muscle relaxation, and jaw tone should be assessed to determine the ability to intubate. If after waiting 60 seconds the dog's level of anesthesia is not sufficient for successful intubation, additional TELAZOL may be administered; the total dose should not exceed 2 mg/lb (4.4 mg/kg) body weight.

L. Route of Administration

Intravenous Injection

M. Species/Class

Dogs

N. Indications

TELAZOL administered intravenously is indicated in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

O. Effect of Supplement

This effect of the supplement is for intravenous administration in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

II. EFFECTIVENESS

Dosage characterization was demonstrated using a pharmacokinetic study and three published articles.

A. Dosage Characterization

In order to determine the key intravenous (IV) pharmacokinetic (PK) parameters, a single dose of tiletamine and zolazepam was administered at 2.2 mg/kg Telazol® to 12 Beagle dogs in a laboratory study. Blood samples were collected from each dog at 3, 7, and 20 minutes; and 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours post-dose. The concentration of tiletamine and zolazepam was measured in canine plasma using a validated LC-MS/MS assay. The tiletamine and zolazepam PK parameters were estimated for each dog using a non-compartmental analysis and nominal sample times and doses.

Table 1: Summary of mean PK parameters for Tiletamine and Zolazepam administered at 2.2 mg /kg Telazol® IV to dogs

Compound	Parameter	Mean	Standard Deviation
Tiletamine (1.1 mg/kg)	CL (mL/kg/h)	6223.89	1022.10
	V_{ss} (mL/kg)	3314.92	840.66
	C_0 (ng/mL)	1018	424.233
	$AUC_{0\text{-}t(last)}$ (ng•h/mL)	178.14	25.94
	$AUC_{0\text{-}\infty}$ (ng•h/mL)	180.99	26.54
	$t_{1/2\lambda}$ (h)	0.87	0.28
Zolazepam (1.1 mg/kg)	CL (mL/kg/h)	1993.25	275.79
	V_{ss} (mL/kg)	604.70	68.21
	C_0 (ng/mL)	2594.41	394.31
	$AUC_{0\text{-}t(last)}$ (ng•h/mL)	561.44	77.16
	$AUC_{0\text{-}\infty}$ (ng•h/mL)	562.47	77.43
	$t_{1/2\lambda}$ (h)	0.41	0.09

CL=clearance
V_{ss}= steady state volume of distribution
C_0= initial concentration
$AUC_{0\text{-}t(last)}$ = area under the curve to last measured concentration
$AUC_{0\text{-}\infty}$= area under the curve extrapolated to infinity
$t_{1/2}$= half-life lambda

Three published studies support the dose and route of administration for intravenous (IV) use of Telazol® for anesthesia induction in dogs.

A published study entitled "Comparing the effects of intravenous (IV) and intramuscular (IM) administration of Telazol® in dogs" (Tracy et al. 1988) used a crossover study design. Ten healthy Beagles were administered Telazol® on 2 occasions separated by a 1 week wash-out period. The dose was 9.9 mg/kg, the approved IM dose indicated for minor procedures. Telazol® was administered IM to 5 dogs and IV to the remaining 5 dogs during the first leg of the crossover. During the second leg, dogs received the alternate route of administration. No other drugs were administered. The study demonstrated that IV administration of Telazol® resulted in a faster onset of action, shorter recovery time, and a more consistent level of anesthesia compared to intramuscular (IM) administration of Telazol®.

A second published study entitled "Testing low doses of intravenous Telazol® in canine practice" was conducted in 100 client-owned dogs (Donaldson et al. 1989) and used lower doses (2 or 4 mg/kg body weight) of IV Telazol®. Fifty-five dogs

received Telazol® alone for induction prior to inhalant anesthesia. The study also evaluated IV Telazol® in 45 dogs when administered in conjunction with preanesthetics (phenothiazine or phenothiazine/opioid) to improve the quality of anesthetic induction.

Dogs retained active palpebral reflexes and some jaw tone though the jaw tone was significantly reduced. Some dogs that received 2 mg/kg of Telazol® without preanesthesia required an additional 2 mg/kg dose to complete intubation. All dogs that received acepromazine (ace)/opioid received 2 mg/kg of Telazol® IV and were easily intubated. One of these dogs required additional Telazol® (1 mg/kg) to facilitate the transition to inhalant anesthesia. Dogs had increased heart rates and altered respiratory patterns after Telazol® administration at both dosages. A brief period of apnea followed by slow shallow breathing was observed. The authors concluded that a low dose (2-4 mg/kg) of Telazol® IV was relatively safe and effective as an induction agent prior to inhalant anesthesia and that preanesthesia improved the quality of anesthetic induction.

A third published study entitled "Cardiorespiratory Effects of the Intravenous Administration of Tiletamine-Zolazepam to Dogs" (Hellyer et al. 1989) showed that an IV dose lower than the IM dose on the approved Telazol® label could be used for induction of anesthesia with satisfactory cardiovascular safety.

In a two-part study, 18 dogs were assigned to one of 3 groups receiving Telazol® IV at doses of 6.6, 13.2, and 19.8 mg/kg. The dogs received the same IV doses again during part 2 of the study. In the first part, the anesthetic and respiratory effects of Telazol® administered IV were evaluated after its administration to un-preanesthetized dogs. In the second part, hemodynamic data were recorded in instrumented dogs under isoflurane anesthesia. In Part 1, Telazol® produced rapid induction, good quality anesthesia (15-40 minutes duration), and fair to good recovery. Recovery was significantly shorter in the 6.6 mg/kg dose group. The hemodynamic effects of Telazol® administered IV observed in part 2 of the study included increased heart rate and cardiac output and decreased arterial blood pressure and peripheral vascular resistance.

These 3 publications collectively indicated that Telazol® administered IV at 2.2-4.4 mg/kg was an acceptable dose and route of administration for the evaluation of induction prior to inhalant anesthesia, to be confirmed in the field effectiveness study.

References:

Donaldson LL, McGrath CJ, Tracy CH. Testing low doses of intravenous Telazol in canine practice. Veterinary Medicine 1989; 84(12):1202-1207.

Hellyer P, Muir WW, Hubbell JA, Sally J. Cardiorespiratory Effects of the Intravenous Administration of Tiletamine-Zolazepam to Dogs. Veterinary Surgery 1989;18(2):160-165.

Tracy CH, Short CE, Clark BC. Comparing the effects of intravenous and intramuscular administration of Telazol. Veterinary Medicine January 1988, 104-111.

B. Substantial Evidence

1. Multi-site Field Safety and Effectiveness

Title: Field Efficacy and Safety of Tiletamine HCl and Zolazepam HCl (TELAZOL) Administered Intravenously for Induction of Anesthesia Followed by Maintenance with an Inhalant Anesthetic in Dogs (Study No. A161C-US-14-481)

Study Dates: April-July 2015

Study Locations:
Lawrence, KS
Zachary, LA
Battle Creek, MI
Grand Rapids, MI
Metairie, LA
Quakertown, PA

Study Design:
Objective: Demonstrate the effectiveness of Telazol® administered IV at a dosage of 2.2-4.4 mg/kg for induction of anesthesia followed by maintenance with inhalant anesthesia. The primary effectiveness endpoint was the ability to successfully intubate the dog (yes/no).

Confirm that the use of Telazol® administered IV (2.2-4.4 mg/kg) for induction of anesthesia in dogs was safe and effective when used in combination with preanesthetics from the opioid, phenothiazine, and alpha2-agonist drug classes and with isoflurane and sevoflurane inhalant anesthetics.

Study Animals: One hundred and forty-four dogs were enrolled in the study. Eighty-four (58.3%) of the dogs were female; 49 were spayed females and 35 were intact females that underwent ovariohysterectomy during the study. Sixty (41.7%) dogs in the study were male; 30 were neutered males and 30 were intact (with 23 castrated during the study and 7 remaining intact). The mean age was 5 years with a minimum age of 4 months and maximum of 14 years. Dogs ranged from 1.2- 85.5 kg body weight.

A variety of pure breed and mixed breed dogs were enrolled: 68.1% were pure bred dogs and 31.9% were mixed breeds. The breeds most commonly enrolled included Labrador Retrievers (10.5%), Pit Bull Terriers (9.1%), Chihuahuas (5.6%), Standard or Miniature Poodles (5.6%), Golden Retrievers (4.9%) and Dachshunds (4.2%).

Experimental Design:
Inclusion Criteria:
- The owner must have given Informed Consent to allow their dog to participate.
- The dog is intended to be sedated and intubated to facilitate a non-emergency procedure requiring inhalant anesthesia for at least 30 minutes.

- The dog qualifies as a category I or II according to the American Society of Anesthesiologists (ASA) Anesthetic Classification for Small Animals.
- Dogs must be at least 16 weeks of age.
- The dog must have a satisfactory physical condition as examined by a study investigator at screening, and have no clinically significant hematological or clinical chemistry abnormalities from the screening blood tests.
- The dog must have fasted for a minimum of 12 hours prior to preanesthetic administration.

Exclusion Criteria:

- The dog has a recent history of breeding, is pregnant or is lactating.
- The dog is grossly obese or emaciated.
- The dog has signs of systemic disease such as respiratory, renal, pancreatic, or hepatic disease (based on clinical and laboratory screening).

Randomization: The study was conducted using a parallel design with 6 preanesthetic/maintenance treatment groups (T01-T06) and a total of 144 dogs. Each study site enrolled 24 dogs with a pre-determined number of dogs (8) assigned to each of 3 preanesthetic groups. Once 8 dogs were enrolled in a group at a given site, the group was closed to further enrollment at that site.

Dogs were not randomized to preanesthetic group but were assigned by the Investigator who used his professional judgment to determine which was most suitable for a given dog based on its individual characteristics and anesthetic needs.

Masking: None

Treatment Groups: Dogs enrolled in the study were assigned to one of three preanesthetic groups by the Investigator:

- Phenothiazine (acepromazine) + opioid
- Opioid alone
- Alpha2-agonist (Dexmedetomidine) + opioid

Table 2: Treatment (Tx) group by preanesthetic, induction agent, maintenance drug, and number of cases

Tx Group	Preanesthetic Group	IV Induction Drug and Dose (mg/kg)	Inhalant Anesthetic*	# of Cases
T01	Phenothiazine + Opioid	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Isoflurane	30
T02	Opioid alone	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Isoflurane	32
T03	Alpha$_2$-agonist + Opioid	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Isoflurane	34
T04	Phenothiazine + Opioid	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Sevoflurane	16
T05	Opioid alone	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Sevoflurane	16
T06	Alpha$_2$-agonist + Opioid	Tiletamine/zolazepam 2.2-4.4 mg/kg IV	Sevoflurane	16

*The ratio of dogs receiving isoflurane to sevoflurane inhalant anesthesia was 2:1.

The preanesthetic was administered intramuscularly (IM) approximately 20 minutes prior to induction of anesthesia with Telazol®. Either isoflurane or sevoflurane inhalant anesthetic was used for maintenance anesthesia. Two thirds (sites 01-04) of the study sites used isoflurane for inhalant anesthesia and one third (sites 05-06) used sevoflurane. All dogs from any one study site received the same inhalant anesthetic. For the study overall, the ratio of dogs receiving isoflurane to sevoflurane inhalant anesthesia was 2:1. The Investigator chose the opioid from the list in the study protocol. Investigators used dexmedetomidine as the alpha2-agonist or acepromazine as the phenothiazine preanesthetic.

Procedures: Dogs underwent a variety of surgical and non-surgical non-emergency procedures and were maintained under inhalant anesthesia for at least 30 minutes.

Table 3: Procedures by number and percent of total

Procedure Type	n*	%
Dental cleaning/prophylaxis	37	25.7
Ovariohysterectomy	31	21.5
Dental with extractions, gingivectomy, ultrasound, mass removal, or dew claw removal	27	18.8
Castration	18	12.5
Mass/lump/growth/tumor removal	14	9.7
Castration with dental, hernia repair, or dew claw removal	5	3.5
Ovariohysterectomy with dental, mass removal, or hernia repair	4	2.8
Cystotomy	2	1.4

*One each: Laceration, aural hematoma, radiographs, tail amputation, abdominal hernia repair, entropion repair

Housing: Dogs were either housed with their owners or housed overnight at the veterinary hospital prior to study enrollment. Following completion of the procedure, dogs were discharged to the home environment or housed overnight at the veterinary hospital at the discretion of the Investigator.

Drug administration: Telazol® (tiletamine and zolazepam for injection) sterile injectable solution (100 mg/mL when reconstituted) was used for induction in all treatment groups (commercially marketed Telazol®). Telazol® is available in individual vials of 5 mL solution when reconstituted (100 mg/mL). The addition of 5 mL diluent produces a solution containing the equivalent of 50 mg tiletamine base, 50 mg zolazepam base and 57.7 mg mannitol per milliliter.

All dogs received Telazol® as the induction drug. The target dose of Telazol® was 2.2-4.4 mg/kg body weight. The Investigator calculated the volume of Telazol® to be drawn into the syringe based on the dog's body weight and the maximum (4.4 mg/kg) dose; the volume in mL was recorded. Telazol® was administered to achieve a level of anesthesia sufficient for endotracheal intubation as judged by muscle relaxation, level of consciousness, and jaw tone of the patient.

Dosing and Intubation Procedure: Telazol® was administered IV through an in-dwelling catheter 'to effect'. The Investigator administered approximately one half of the Telazol® in the syringe by slow IV injection over 30-45 seconds. After administering half of the syringe, the Investigator waited 30-60 seconds and assessed the dog's level of sedation and ability to be intubated. If sufficient, the Investigator attempted to intubate the dog. If after waiting 60 seconds the dog's level of anesthesia was not sufficient for successful intubation, the Investigator or designee slowly administered additional Telazol® and made another attempt to intubate the dog. If the administration of additional Telazol® did not permit intubation, the dog was induced by mask administration of inhalant anesthetic.

Measurements and Observations: The primary variable was assessed by anesthesia sufficient for intubation as judged by muscle relaxation, level of consciousness, and jaw tone. To satisfy secondary objectives of the study, quality of induction, recovery, and overall quality of anesthesia were subjectively evaluated. Physiologic variables were also assessed. Dogs were monitored preoperatively, during the procedure, and in recovery by recording heart rate and rhythm, respiratory rate and rhythm, and body temperature. Oxygen saturation, blood pressure (BP), and electrocardiograms were recorded during the period of inhalant anesthesia.

Statistical Methods: The primary effectiveness variable was the assessment of the ability or inability to successfully intubate the dog following administration of Telazol®. A successful intubation was defined as intubation without the need for inhalant anesthetic administered by mask prior to intubation. Each dog was considered either a successful intubation or an intubation failure. Successful intubation was summarized by treatment group. The dosage (mg/kg) of intravenous Telazol® required for successful intubation by preanesthetic treatment group was summarized (mean, standard deviation, minimum and maximum) to confirm the proposed dosage of 2.2-4.4 mg/kg body weight. Physiologic variables related to the safety of Telazol® were

summarized by treatment group and time point. Subjective assessments of induction, recovery, and overall anesthesia quality were summarized by treatment group.

Results: Primary Variable of Effectiveness = Intubation: Successful intubation was achieved with Telazol® administered intravenously at a dosage of 2.2-4.4 mg/kg in 142/144 dogs (98.6%). The two dogs that could not be intubated were both pre-medicated with an opioid alone.

Telazol® Dose Confirmation: The overall results confirm the proposed dose range. For 11 small dogs (< 10 kg body weight) the maximum Telazol® volume was drawn in the syringe to the nearest 0.1 mL resulting in a maximum Telazol® dose slightly greater than 4.4 mg/kg. One dog (3.65 kg) received the highest dose of Telazol® (5.5 mg/kg), was intubated, and experienced a 'normal' anesthetic and surgical period and recovery. The lowest dose was 0.592 mg/kg (16.9 kg); this dog was also intubated satisfactorily with a normal anesthetic/surgical/recovery period.

Table 4. Summary of Telazol® Dosage (mg/kg) by Treatment Group

Tx Group	Preanesthetic Drug(s)	Inhalant Anesthetic	n	Mean	Standard Deviation	Min	Max
T01	Phenothiazine + Opioid	Isoflurane	30	2.507	0.854	1.117	4.819
T02	Opioid alone	Isoflurane	32	2.789	0.999	1.250	4.938
T03	Alpha2-agonist + Opioid	Isoflurane	34	2.012	0.502	0.592	2.703
T04	Phenothiazine + Opioid	Sevoflurane	16	3.120	0.995	2.128	4.455
T05	Opioid alone	Sevoflurane	16	3.855	1.042	2.083	4.773
T06	Alpha2-agonist + Opioid	Sevoflurane	16	3.249	1.193	2.033	5.479

Quality of Induction: On a scale of acceptable, intermediate, and unacceptable, induction quality was subjectively evaluated as acceptable in 131/143 dogs (91.6%) and intermediate in 12/143 (8.4%).

Time to onset of anesthesia (time to intubation): The mean time to onset of anesthesia sufficient for intubation was 2 minutes across all treatment groups (minimum <1 minute; maximum 11 minutes). Dogs preanesthetized with an opioid alone experienced a longer time to onset of anesthesia.

Overall Quality of Anesthesia: The overall assessment of anesthesia (on a scale of excellent, good, fair, or poor) including the time from induction to full recovery was scored excellent or good in 128/144 dogs (88.9%). In 3 dogs (2.1%) anesthesia quality was rated as poor and for these dogs, recovery was also rated as poor.

Recovery (scored as good, fair, or poor): Seventy-five percent of dogs (108/144) had a 'good' recovery, 18.1% (26/144) had a fair recovery and 6.9% (10/144) had a poor recovery. Preanesthesia with an opioid alone

accounted for 6/10 (60%) of the poor recoveries. Recovery times (vaporizer turned 'off' to standing) varied widely across all 6 treatment groups (minimum 13 minutes; maximum 275 minutes). Recovery times vary widely and are subject to many variables besides preanesthesia, including procedure, investigator, and individual animal responses. Longer times were observed in the phenothiazine + opioid groups (T01 and T04). None were described by the investigators as 'prolonged'.

Physiological Variables: Measurements of heart rate (HR), respiratory rate (RR), body temperature (T), oxygen saturation (SpO_2) and blood pressure (BP; indirect) during anesthetic induction, maintenance, and recovery resulted in satisfactory hemodynamic data. These measurements showed that the administration of Telazol® IV did not impact these variables in an adverse way. Differences between treatment groups were most obvious in the alpha$_2$-agonist + opioid groups due to the potent effects of alpha$_2$-agonists. The effects were not unexpected or severe.

Post-induction apnea (time from successful induction to first inspiration ≥30 seconds) was observed in 49.3% of dogs across all treatment groups with a mean duration of one minute. Apnea occurred in all treatment groups for similar durations. The highest overall frequency and duration of post-induction apnea was in the alpha$_2$-agonist + opioid groups.

Overall, 36 dogs received assisted ventilation. Assisted ventilation was needed most frequently early in the procedure (at procedure start, possibly after an apneic period) then decreased in frequency as the procedure continued. The alpha$_2$-agonist + opioid/isoflurane group required assisted ventilation in the largest number of dogs (17 of 36).

Sixteen dogs experienced oxygen saturation (SpO_2) ≤90 mmHg: 7 in the alpha$_2$-agonist + opioid groups, 6 in the phenothiazine + opioid groups and 3 in the opioid alone groups. Not all dogs that received assisted ventilation showed SpO_2 ≤90.

Table 5: Number of Dogs with SpO2 ≤90 by Treatment (Tx) Group, Preanesthetic, and Inhalant Anesthetic

Tx Group	Preanesthetic drug(s)	Inhalant Anesthetic	Number of dogs*
T01	Phenothiazine + opioid	Isoflurane	4
T02	Opioid alone	Isoflurane	2
T03	Alpha$_2$-agonist + opioid	Isoflurane	1
T04	Phenothiazine + opioid	Sevoflurane	2
T05	Opioid alone	Sevoflurane	1
T06	Alpha$_2$-agonist + opioid	Sevoflurane	6

*Total number = 16 dogs.

Most dogs received supplemental heat during surgery. Twenty-seven dogs experienced temperatures ≤96°F at one or more time points, ranging across all 6 dose groups but concentrated in the isoflurane maintenance groups.

Twenty-five dogs had T ≥103°F during the study, with 12 of these occurring prior to preanesthetic administration only. Of the remaining 13 dogs, 7 were in

the alpha$_2$-agonist + opioid groups, 5 were in the opioid alone group, and 1 in the acepromazine/opioid group.

Fifty-nine dogs had mean BP values ≤60 mmHg. These values are spread among all treatment groups. No dogs were reported with adverse reactions due to hypotension or hypertension in any dose groups. Elevated or low BP values were transient.

Ventricular premature depolarizations were noted in 3 dogs all of which received alpha$_2$-agonist + opioid as preanesthetics, Telazol® for induction, and isoflurane for maintenance anesthesia. This transient rhythm disturbance is not uncommon in dogs receiving alpha$_2$-agonists or isoflurane so the relationship to Telazol® cannot be determined. One dog in the phenothiazine + opioid; isoflurane treatment group (T02) showed ST depression that could have been due to cardiac hypoxia. The dogs recovered normally.

Concomitant medication: The most commonly used concomitant medications were intravenous fluid solutions (Lactated Ringer's solution, sodium chloride, and electrolyte combinations) administered during the procedure and non-steroidal anti-inflammatory medications used for postoperative analgesia. Penicillin was also commonly administered either before or after the procedure. A variety of vaccines and antiparasitics were administered, consistent with routine canine practice.

Adverse Reactions: Adverse reactions (ARs) that occurred during the period of hospitalization or from the time of discharge to the follow-up contact (3 ±1 days after the date of the procedure) were recorded.

No mortalities or serious ARs were reported during the study and all 144 enrolled dogs completed the study. Including events that occurred during the study and the 3-day follow up period, 16 ARs were reported as follows: nystagmus (5), emesis (4), diarrhea (2), and 1 occurrence each of hypersalivation, urticarial, anorexia, hyperthermia, and lethargy. All abnormal health events were resolved by the end of the follow up period.

One dog with hyperthermia was reported as an AR (T03). The dog became excitable during recovery and its temperature elevated to 105.7°F. The dog responded well to treatment with IV fluids at room temperature given as a bolus, application of cool towels to the skin, and cooling using fans. The temperature returned to normal in approximately 45 minutes.

Table 6: Adverse Reactions by Treatment Group

Adverse Reaction	T01	T02	T03	T04	T05	T06	Total
Nystagmus	0	0	0	2	1	2	5
Emesis	1	1	1	0	0	1	4
Diarrhea	0	0	1	0	0	1	2
Hypersalivation	0	0	0	1	0	0	1
Urticaria	0	0	0	1	0	0	1
Anorexia	0	0	0	0	0	1	1
Hyperthermia	0	0	1	0	0	0	1
Lethargy	0	0	0	0	0	1	1
Total	1	1	3	4	1	6	16

Conclusion: The field study results demonstrate the effectiveness and field safety of Telazol® when administered IV to dogs, at the dose range of 2.2-4.4 mg/kg, for induction of anesthesia followed by maintenance with an inhalant anesthetic in dogs.

III. TARGET ANIMAL SAFETY

A. Preanesthetic Compatibility Study

Title: Evaluation of Cardiovascular and Respiratory Safety of TELAZOL when Administered Intravenously to Beagle Dogs Pre-medicated with Commonly Used Pre-anesthetic Agents at Clinically Relevant Doses (Study No. A360N-US-15-554).

Study Dates: June 10, 2015 to September 15, 2016

Study Location: Columbus, OH

Study Design:

Objective: The objective of the GLP-compliant study was to evaluate the cardiovascular and respiratory safety and pharmacokinetics (PK) of Telazol® when administered intravenously to dogs preanesthetized with acepromazine, dexmedetomidine (dex), or butorphanol (butorph) at a dose sufficient to support intubation. The interactions between Telazol® and the individual pre-anesthetic agents were evaluated.

Study Animals: There were 6 healthy Beagle dogs (3 males and 3 females) per group. The dogs were greater than 8 months of age and weighed 5.6 to 9.4 kg. The dogs were fitted with a telemetry device that captured systemic arterial blood pressure, electrocardiogram (ECG), and body temperature.

Experimental Design: The cross-over study included 6 periods with at least a 7-day washout between periods. Each period, the dog received a different 1 of the 6 intramuscular (IM) preanesthetics prior to the Telazol® administration as described in Table 6 below. The dose assignments were determined using a balanced Latin square design with period and dog as the blocking factors.

Table 7. Treatment Groups and Preanesthetic Doses

Treatment Group	Preanesthetic Dose (intramuscular)	Inhalant
0.9% Saline	0.1 mL/kg	Isoflurane
Acepromazine (low dose)	0.11 mg/kg	Isoflurane
Acepromazine (high dose)	1.1 mg/kg	Isoflurane
Dexmedetomidine (low dose)	125 mcg/cm^2 BSA[a]	Isoflurane
Dexmedetomidine (high dose)	375 mcg/cm^2 BSA[a]	Isoflurane
Butorphanol	0.4 mg/kg	Isoflurane

[a] BSA = Body Surface Area

Drug Administration: Twenty-five minutes after administration of the preanesthetic, Telazol® was administered at 2.2 mg/kg to all dogs, in all treatment groups, using an indwelling intravenous (IV) catheter. An additional 2.2 mg/kg of Telazol® administered IV was permitted to achieve oro-tracheal intubation.

Measurements and Observations: The following variables were recorded or calculated at the following targeted time points: prior to preanesthetic administration; approximately 25 minutes after preanesthetic administration; 5, 10, 15, 20, 30, 40, 50, and 60 minutes after isoflurane administration; and every 10 minutes after termination of isoflurane until the dog was able to walk without ataxia.

- Heart rate; heart rhythm from ECG waveform; systolic, diastolic, and mean arterial pressures (MAP); and body temperature from the telemetry system.
- Respiratory rate, quality of respiration, end tidal CO2, and SpO2.
- Palpebral and corneal reflex and eye position for assessment of anesthetic plane.
- Anesthetic plane.

The following parameters were also recorded (or calculated) as applicable:

- Time of preanesthetic administration, Telazol® administration, head drop, onset of sternal and lateral recumbency, intubation, isoflurane administration, isoflurane termination, first head lift, first sign of recovery (purposeful movement), first attempt to attain sternal recumbency, sternal recumbency, first attempt to stand, standing, and walking without ataxia.
- Total dose of test article administered for successful intubation and number of intubation attempts.
- Time from preanesthetic administration to head drop, onset of sternal recumbency, onset of lateral recumbency.
- Time from Telazol® administration to head drop, onset of sternal recumbency, onset of lateral recumbency, time of intubation.
- Time from termination of isoflurane to head lift, swallow, extubation, first sign of recovery (purposeful movement), first attempt to attain sternal recumbency, sternal recumbency, first attempt to stand, standing, and walking without ataxia.
- Time from intubation to start of isoflurane.
- Duration of recumbency; from onset of lateral recumbency to first attempt to attain sternal recumbency.

- Scores of the quality of induction, anesthesia, and recovery from anesthesia.
- Behavioral observation during induction and recovery.
- Adverse reactions; apnea (lack of inspiratory effort [apnea] for 60 seconds), SpO2 <85%, tachycardia/bradycardia (HR 180/50 bpm), hypertension/hypotension (MAP 160/50 mmHg), heart arrhythmias (except sinus arrhythmias), nausea, death or other unexpected events.

Plasma concentrations of tiletamine and zolazepam were measured at the time of intubation, end of isoflurane, and after anesthesia when dogs were able to walk without ataxia.

Statistical Methods: The primary variables were evaluated by group using descriptive statistics, such as means and standard deviations, minimum and maximum using charts or tables.

Results:

Following Telazol® administration, all dogs, in all treatment groups, achieved a successful anesthetic plane, were oro-tracheally intubated, and induced to isoflurane anesthesia uneventfully.

No information on the dose-sparing of Telazol® was obtained during the study because all dogs were administered the full initial half-dose (2.2 mg/kg); Telazol® was not administered 'to effect'. The average total dose of Telazol® administered to the dogs was 2.6 mg/kg in the saline group and 2.2 mg/kg in all other treatment groups. One dog in the saline group required more than the initial 2.2 mg/kg bolus to achieve intubation.

Without preanesthesia (saline group), dogs retained a strong cough reflex, chewing motions, tachycardia, and increased muscle tone during intubation. With preanesthesia, half of the dogs in the high dose dexmedetomidine group had no laryngeal reflex response to intubation and all experienced post-intubation apnea. The post-intubation apnea suggests that the 2.2 mg/kg dose of Telazol® was higher than necessary in some treatment groups.

All dogs dropped their heads, became sternal and lateral within 1 minute following Telazol® administration. Intubation was achieved in 1 attempt in all dogs in all treatment groups except 1 dog in the saline group. This dog needed 4.3 mg/kg for intubation and 4 attempts. The administration of a preanesthetic improved the quality score of intubation.

There was no change in body temperature in all dogs with the use of a warm water circulating blanket or towels. Body temperatures tended to decrease during recovery from anesthesia but stayed within the normal physiological range.

The occurrence and severity of adverse reactions (e.g., apnea) following Telazol® administration and intubation revealed differences among treatment groups based on the type and dose of preanesthetic. The hemodynamic and respiratory changes observed were typical of each preanesthetic medication used in combination with Telazol®. Acepromazine and isoflurane administration decreased arterial blood pressure. Dexmedetomidine decreased heart rate, and intubation transiently increased heart rate and/or blood pressure due to sympathetic stimulation. Mild to

severe respiratory depression (decrease in respiratory rate and increase in end tidal CO_2) was observed following administration of Telazol® in all groups. When Telazol® /isoflurane anesthesia was initiated, all dose groups had some dogs with bradypnea over the next few time points. The incidence of bradypnea in dogs in the dose groups (from lowest to highest incidence) was: saline group, acepromazine low dose group, acepromazine high dose group, butorphanol group, and the dexmedetomidine high and low dose groups. Apnea (≥60 seconds) was observed in all treatment groups following Telazol® administration/intubation except in the saline group. Adverse events included apnea or bradypnea that required manual ventilation until spontaneous resolution.

Mild disorientation did occur during recovery from isoflurane anesthesia after 60 minutes of isoflurane anesthesia.

The geometric mean and range for tiletamine and zolazepam plasma concentrations, respectively are summarized in Tables 7 and 8.

Table 8. Tiletamine Plasma Concentrations (ng/mL) by Treatment and Time Point

Time point[a]	Treatment	N	Geo. mean	Range
Intubation	T01 (Saline)	5[b]	476.73	354-585
Intubation	T02 (Ace low)	6	604.98	367-884
Intubation	T03 (Ace high)	6	920.24	703-1150
Intubation	T04 (Dex low)	6	1296.72	630-1990
Intubation	T05 (Dex high)	6	2130.44	1580-3220
Intubation	T06 (Butorph)	5[c]	534.25	293-736
End isoflurane	T01 (Saline)	5[b]	69.04	55.8-88.2
End isoflurane	T02 (Ace low)	6	72.91	54-94.5
End isoflurane	T03 (Ace high)	6	72.8	54.8-86.2
End isoflurane	T04 (Dex low)	6	59.4	49.4-92.2
End isoflurane	T05 (Dex high)	6	68.38	54.5-88.9
End isoflurane	T06 (Butorph)	5[c]	71.21	55.6-107
Able to walk	T01 (Saline)	5[b]	57.61	37.8-70.6
Able to walk	T02 (Ace low)	6	41.05	26-55.4
Able to walk	T03 (Ace high)	6	21.17	9.17-32.5
Able to walk	T04 (Dex low)	6	40	27.3-57.6
Able to walk	T05 (Dex high)	6	26.26	21.4-30.5
Able to walk	T06 (Butorph)	5[c]	29.81	23.1-38.7

[a] The time points correspond to the time of intubation, end of isoflurane, and after anesthesia when dogs were able to walk without ataxia.
[b] One dog was excluded due to delayed time to intubation
[c] One dog had missing plasma samples

Table 9. Zolazepam Plasma Concentrations (ng/mL) by Treatment and Time Point

Time point[a]	Treatment	N	Geo. mean	Range
Intubation	T01 (Saline)	5[b]	1298.4	1110-1410
Intubation	T02 (Ace low)	6	1442.53	1000-1990
Intubation	T03 (Ace high)	6	2030.06	1810-2520
Intubation	T04 (Dex low)	6	2364.94	1280-3350
Intubation	T05 (Dex high)	6	3625.9	2730-5150
Intubation	T06 (Butorph)	5[c]	1340.13	885-1630
End isoflurane	T01 (Saline)	5[b]	140.25	104-180
End isoflurane	T02 (Ace low)	6	160.6	123-226
End isoflurane	T03 (Ace high)	6	153.36	124-177
End isoflurane	T04 (Dex low)	6	115.01	92.4-163
End isoflurane	T05 (Dex high)	6	139.31	119-179
End isoflurane	T06 (Butorph)	5[c]	144.54	118-226
Able to walk	T01 (Saline)	5[b]	107.78	82.5-118
Able to walk	T02 (Ace low)	6	69.17	41.4-114
Able to walk	T03 (Ace high)	6	20.9	6.55-63.6
Able to walk	T04 (Dex low)	6	79.73	61.4-94.8
Able to walk	T05 (Dex high)	6	44.53	36.8-56.4
Able to walk	T06 (Butorph)	5[c]	43	27.8-60

[a] The time points correspond to the time of intubation, end of isoflurane, and after anesthesia when dogs were able to walk without ataxia.
[b] One dog was excluded due to delayed time to intubation
[c] One dog had missing plasma samples

Preanesthetic treatment with high dose acepromazine and both high and low doses of dexmedetomidine resulted in substantial increases in plasma concentrations of tiletamine and zolazepam at intubation. The increase in the geometric mean tiletamine plasma concentrations was approximately 2X higher for the high dose of acepromazine and 2.7 to 4.5X higher for the low and high doses of dexmedetomidine, respectively, compared to saline. The increase in the geometric mean zolazepam plasma concentrations was 1.5X higher for the high dose acepromazine, and 1.8 to 2.8X higher for the low and high doses of dexmedetomidine, respectively, compared to saline.

Conclusions:
Telazol® administered intravenously at a dose of 2.2 mg/kg along with saline, acepromazine, dexmedetomidine, or butorphanol was safe for induction prior to maintenance using an inhalant anesthetic in dogs. Dogs should be closely monitored for respiratory depression (especially apnea or bradypnea).

IV. HUMAN FOOD SAFETY

This drug is intended for use in dogs. 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

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Telazol®:

FOR USE IN DOGS AND CATS ONLY.

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 Telazol®, when used according to the label, is safe and effective for intravenous administration in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

A. Marketing Status

This product may be dispensed only by or on the lawful order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because veterinary expertise is necessary to administer general anesthesia to dogs, including monitoring for and treatment of any adverse reactions.

B. Exclusivity

This supplemental approval for Telazol® qualifies for THREE years of marketing exclusivity under section 512(c)(2)(F)(iii) of the FD&C Act because the supplemental application included safety and effectiveness studies. This exclusivity begins as of the date of our approval letter and only applies to intravenous administration in dogs for induction of anesthesia followed by maintenance with an inhalant anesthetic.

C. Supplemental Applications

This supplemental NADA required a reevaluation of the safety or effectiveness data in the original NADA (21 CFR 514.106(b)(2)).

D. Patent Information:

For current information on patents, see the Animal Drugs @ FDA database or the Green Book on the FDA CVM internet website.