TELAZOL (tiletamine and zolazepam for injection) IV Induction Claim FAQs

1) Q: What is TELAZOL?
   A: TELAZOL (tiletamine and zolazepam for injection) is a nonnarcotic, nonbarbiturate, injectable anesthetic agent for dogs and cats. Chemically, TELAZOL is a combination of equal parts by weight of base of tiletamine hydrochloride, a dissociative anesthetic and zolazepam hydrochloride, a benzodiazepine with minor tranquilizing properties.

2) Q: Why was TELAZOL developed as a combination product?
   A: TELAZOL was developed as a combination product because tiletamine alone produces a variety of CNS effects including convulsions and muscle rigidity, whereas zolazepam produces belligerence in some individuals. Both effects have been identified as class effects for the individual drugs. The combination has been shown to produce dissociative anesthesia, to a degree not observed with either drug independently. Additionally, the adverse reactions listed above for each drug were eliminated or minimized when the two drugs were used in combination.

3) Q: How is TELAZOL supplied?
   A: TELAZOL is supplied as a desiccated cake in sterile vials. 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. This solution has a pH of 2 to 3.5 and is recommended for deep intramuscular injection in the dog and cat and intravenous injection in the dog.

4) Q: What are the instructions to prepare the TELAZOL solution for administration?
   A: To prepare the TELAZOL solution for administration, add 5 mL sterile water for injection, USP, to each vial. Slight agitation will facilitate complete reconstitution. The resultant solution will contain 100 mg total TELAZOL per one milliliter (50 mg tiletamine and 50 mg zolazepam per mL).

5) Q: Is TELAZOL a DEA controlled substance?
   A: Yes, TELAZOL is a Class III DEA controlled substance. As such, it is necessary to provide special shipping and storage, and to ensure accurate record keeping. Since this is a controlled substance, the Zoetis field force cannot take possession of this product. Please contact the Customer Service Center for shipping instructions.

6) Q: What are the TELAZOL indications and dosages stated in the original FDA approval?
   A: Cats: For restraint or for anesthesia combined with muscle relaxation:
   Dosage: For procedures such as dentistry, treatment of abscesses, foreign body removal and related types of surgery: 9.7 to 11.9 mg/kg (4.4 to 5.4 mg/lb.)
           For minor procedures of short duration requiring mild to moderate analgesia, e.g. repair of lacerations, castration: 10.6 to 12.5 mg/kg (4.8 to 5.7 mg/lb.)
           For ovariohysterectomy and onychectomy: 14.3 to 15.8 mg/kg (6.5 to 7.2 mg/lb.)
           When supplemental doses of TELAZOL are required, such individual supplemental doses should be given in increments that are less than the initial dose, and the total dose given (initial dose plus supplemental doses) should not exceed the maximum allowable safe dose of 72 mg/kg (32.7 mg/lb.).
   Dogs: For restraint and minor procedures of short duration (30 min. avg.) requiring mild to moderate analgesia.
   Dosage: Diagnostic purposes: 6.6 to 9.9 mg/kg (3 to 4.5 mg/lb.) IM
           Minor procedures of short duration, e.g. treatment of lacerations and wounds, castrations and other procedures requiring mild to moderate analgesia: 9.9 to 13.2 mg/kg (4.5 to 6 mg/lb.) IM.
   ➢ Results from TELAZOL anesthesia in dogs given at these dosages IM are better if procedures are completed within one hour and are completed following the administration of a single dose.
When supplemental doses of TELAZOL are required, such individual supplemental doses should be less than the initial dose, and the total dose given (initial dose plus supplemental dose or doses) should not exceed 26.4 mg/kg (12 mg/lb).

7) Q: What does the new TELAZOL claim allow for?
   A: The new claim provides for use as an intravenously administrated induction agent to general anesthesia followed by maintenance with an inhalant anesthetic in dogs.
   Dosage: 2.2-4.4 mg/kg (1-2 mg/lb).

8) Q: Are there minimum and/or maximum age limitations for animals that receive TELAZOL?
   A: There are no stated minimum or maximum ages stated for dogs or cats that receive TELAZOL. However the dosage should be reduced when used in geriatric animals.

9) Q: Why did Zoetis decide to get a new claim for TELAZOL?
   A: TELAZOL was initially approved in 1984. At that time, providing a single combination drug of a dissociative and benzodiazepine for sedation for short general anesthetic procedures was an innovative way to meet a need for veterinary-specific anesthetic agents. Since that time, the practice of anesthesia has evolved to balanced anesthesia, where multiple drugs are used during the different phases of anesthesia to minimize the drug dosages, thereby improving safety and comfort of the patient. The original approval of TELAZOL did not allow it to fit into today's anesthetic protocols. To increase the clinical relevancy of TELAZOL, we consulted with various experts in veterinary anesthesia and reviewed the literature and determined that an IV induction claim would provide the best opportunity for TELAZOL to fit into a balanced anesthetic protocol for dogs.

10) Q: What are the administration instructions for TELAZOL IV Induction?
    A: TELAZOL should be administered intravenously at a dosage of 1-2 mg/lb body weight (2.2-4.4 mg/kg) for induction of anesthesia followed by maintenance with an inhalant anesthetic. 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.

11) Q: Is this new claim for both dogs and cats?
    A: The IV induction claim applies to dogs. All studies conducted to support the claim were conducted in dogs. We did not generate data for TELAZOL IV induction dosage for cats.

12) Q: What types of studies were conducted to support the use of TELAZOL as an induction agent administered intravenously in dogs?
    A: Three studies were conducted to support the use of TELAZOL as an IV induction agent in the dog. Table 1 lists the key components of each of these studies.
    The three Studies are
    1) Field Efficacy and Safety of tiletamine and zolazepam for injection (TELAZOL) administered Intravenously for induction of anesthesia followed by maintenance with an inhalant anesthetic in dogs
    2) Pharmacokinetics of tiletamine and zolazepam administered at 2.2 mg/kg to dogs
    3) Evaluation of cardiovascular and respiratory safety of Telazol when administered intravenously to beagle dogs premedicated with commonly used pre-anesthetic agents at clinically relevant doses
### Table 1: Summary of Studies Conducted to Support the use of TELAZOL as an Intravenous Induction Agent in dogs

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Multi-center Open Label Field Efficacy &amp; Safety</th>
<th>IV Pharmacokinetics</th>
<th>Drug Preanesthetic Interaction Safety; Target Animal Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective</td>
<td>Demonstrate effectiveness of TELAZOL as an induction agent prior to maintenance with gas inhalant.</td>
<td>Estimate the key PK parameters of tiletamine and zolazepam in dog plasma after receiving an IV dose of 2.2 mg TELAZOL/kg body weight.</td>
<td>Evaluate the CV &amp; respiratory safety of TELAZOL IV, in dogs premedicated with IM acepromazine, dexmedetomidine, or butorphanol.</td>
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<tr>
<td>Confirm TELAZOL® administered IV for induction in dogs was safe/ effective when used in combination with various preanesthetics and inhalant anesthetics.</td>
<td></td>
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<td>Access interactions between TELAZOL and the individual pre-anesthetic selected.</td>
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<tr>
<td>Animals</td>
<td>144 dogs; 84 F (49 spayed/35 intact); 60 M (30 Neutered; 30 intact); Mean age: 5 years (4 m-14 y); Weight: 1.2-85.5 kg; 68.1% were pure bred dogs; 31.9% were mixed breeds.</td>
<td></td>
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<tr>
<td>TELAZOL Dosage</td>
<td>Target dose: 2.2-4.4 mg/kg BW; IV</td>
<td>2.2 mg/kg body weight, IV</td>
<td>2.2 mg/kg IV, + 2.2 mg/kg if required</td>
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<tr>
<td>Administration or Study Design</td>
<td>The maximum (4.4 mg/kg) dose for a dog was drawn. ~1/2 the volume of TELAZOL was administered slowly IV, over 30-45 seconds. After waiting another 30-60 sec, intubation was attempted. If after 60 seconds the dog was not sufficiently anesthetized to allow for intubation, additional TELAZOL® was administered and intubation was attempted again. If intubation was not successful at this point the dog was induced by mask with inhalant anesthetic.</td>
<td>2 mL of blood was collected from each dog at 3, 7, 20, minutes, 1, 1.5, 2, 2.5, 3, 4, 6, 8 hours post-dose. The concentration of tiletamine and zolazepam was measured in canine plasma using a validated LC-MS/MS assay.</td>
<td>0.9% Saline 0.1 mL/kg BW</td>
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<td></td>
<td>12 beagle dogs (8 female, 4 male) aged 19.8 – 20.2 months and weighing 8.4 to 12 kg.</td>
<td></td>
<td>0.11 mg/kg BW</td>
</tr>
<tr>
<td></td>
<td>6 healthy Beagle dogs (3 male, 3 female) greater than 8 months of age and weighing 5.6 – 9.4 kg</td>
<td></td>
<td>1.1 mg/kg BW</td>
</tr>
<tr>
<td>Groups</td>
<td>Preanesthetic*</td>
<td>Inhalant*</td>
<td>125 mcg/m2 b</td>
</tr>
<tr>
<td></td>
<td>G1: Acepromazine/opioid</td>
<td>Isoflurane</td>
<td>375 mcg/m2</td>
</tr>
<tr>
<td></td>
<td>G2: Opioid alone</td>
<td>or Sevoflurane</td>
<td>Butorphanol 0.4 mg/kg BW</td>
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<tr>
<td></td>
<td>G3:Dexmedetomidine/opioid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Results</td>
<td>Successful intubation: 142/144 (98.6%)**</td>
<td>Quality of induction: Acceptable in 131/143 dogs (91.6%) and intermediate in 12/143 (8.4%); unacceptable 0/143 (0%)</td>
<td>All dogs were successful intubated.</td>
</tr>
<tr>
<td></td>
<td>Dosage confirmed at 2.2-4.4 mg/kg.</td>
<td>Overall Quality of Anesthesia: Excellent or good in 128/144 dogs (88.9%); fair in 13/144 (9.0%); poor in 3/144 (2.1%)</td>
<td>All dogs were induced to anesthesia</td>
</tr>
<tr>
<td></td>
<td>Quality of Induction: Acceptable in 131/143 dogs (91.6%) and intermediate in 12/143 (8.4%); unacceptable 0/143 (0%)</td>
<td>Recovery Quality: Good in 108/144 (75%) of dogs: fair in 26/1441(8.1%); poor in 10/144 (6.9)***</td>
<td>Mild to severe respiratory depression was observed after 2.2 mg/kg of TELAZOL and each pre-anesthetic agent</td>
</tr>
<tr>
<td></td>
<td>Physiological parameters showed satisfactory hemodynamic response and demonstrated TELAZOL® IV did not impact these variables in an adverse way.</td>
<td>Physiological parameters were typical of each pre-anesthetic medication. Acepromazine and isoflurane decreased BP, dexmedetomidine decreased HR, and intubation transiently increased HR and/or blood pressure (sympathetic stimulations).</td>
<td>The dose sparing ratio did not differ among treatment groups</td>
</tr>
<tr>
<td></td>
<td>Post-induction apnea (mean duration-1 m) was observed in 49.3% of dogs across all treatment groups.</td>
<td></td>
<td>Physiological changes were typical of each pre-anesthetic medication. Acepromazine and isoflurane decreased BP, dexmedetomidine decreased HR, and intubation transiently increased HR and/or blood pressure (sympathetic stimulations).</td>
</tr>
<tr>
<td>ADRs</td>
<td>Nystagmus (5), emesis (4), diarrhea (2), and one each: hypersalivation, urticarial, anorexia, hyperthermia, and lethargy</td>
<td>N/A</td>
<td>Occurrence and severity of adverse events (i.e., apnea) was similar across treatment groups.</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Confirms the dose range of 2.2-4.4 mg/kg and demonstrates effectiveness and field safety of TELAZOL® when administered IV to dogs for induction of anesthesia by maintenance with an inhalant anesthetic.</td>
<td>The mean Cmax0 and AUC0-t(last) were ~ 2.5 and 3 times, respectively, greater for zolazepam than for tiletamine. The mean T1/2 of tiletamine was ~ 2.5 times longer than for zolazepam. The quantifiable plasma concentrations were up to 2 hours longer.</td>
<td>TELAZOL, 2.2 mg/kg IV, in dogs premedicated with acepromazine, dexmedetomidine or butorphanol produced predictable drug associated responses and effective induction to general anesthesia. Dogs should be closely monitored for respiratory depression and transient tachycardia following intubation. Mild disorientation may occur during recovery from isoflurane anesthesia.</td>
</tr>
</tbody>
</table>

*Each premed was administered ~ 20 minutes prior to induction and given to 1/3 of dogs; isoflurane was given to 2/3 of dogs; sevoflurane to 1/3

** The 2 dogs that were unsuccessfully intubated received opioid alone as the premed

*** Preanesthesia with an opioid alone accounted for 6/10 (60%) of the poor recoveries.
13) Q: What types of procedures were conducted during the Field Efficacy and Safety Study?  
A: The types and frequency and percentage of total of procedures conducted during the Field Efficacy and Safety Study are summarized in Table 2, below.

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental cleaning/prophylaxis</td>
<td>37</td>
<td>25.7</td>
</tr>
<tr>
<td>Ovariohysterectomy</td>
<td>31</td>
<td>21.5</td>
</tr>
<tr>
<td>Dental with extractions, gingivectomy, ultrasound, mass removal, or dew claw removal</td>
<td>27</td>
<td>18.8</td>
</tr>
<tr>
<td>Castration</td>
<td>18</td>
<td>12.5</td>
</tr>
<tr>
<td>Mass/lump/growth/tumor removal</td>
<td>14</td>
<td>9.7</td>
</tr>
<tr>
<td>Castration with dental, hernia repair, or dew claw removal</td>
<td>5</td>
<td>3.5</td>
</tr>
<tr>
<td>Ovariohysterectomy with dental, mass removal, or hernia repair</td>
<td>4</td>
<td>2.8</td>
</tr>
<tr>
<td>Cystotomy</td>
<td>2</td>
<td>1.4</td>
</tr>
</tbody>
</table>

*Additional procedures include one each of the following: Laceration, aural hematoma, radiographs, tail amputation, abdominal hernia repair, entropion repair.

14) Q: What concomitant medications were administered in the Field Efficacy and Safety Study?  
A: The most commonly concomitant medications administered in the Field Efficacy and Safety Study were intravenous fluid solutions (lactated ringers 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.

15) Q: What is the onset of effect for TELAZOL?  
A: Onset of effect is dependent upon route of administration. When TELAZOL is administered intramuscularly, onset of effect ranges from 5-12 minutes. When TELAZOL is administered IV for induction of anesthesia, onset to intubation was approximately 2 minutes.

16) Q: Can TELAZOL be administered to breeding or pregnant dogs or cats?  
A: Because the teratogenic potential of TELAZOL is unknown, it should not be used in pregnant bitches or queens at any stage of pregnancy. Also, a study has shown that TELAZOL crosses the placental barrier and produces respiratory depression in the newborn; therefore, its use for Cesarean section is contraindicated.

17) Q: Can TELAZOL be used in cats or dogs with renal dysfunction?  
A: TELAZOL is excreted predominantly by the kidneys. Preexistent renal pathology or impairment of renal function may be expected to result in prolonged duration of anesthesia. TELAZOL is not recommended for use in cats with renal insufficiency.

18) Q: Are there other patients that should not receive TELAZOL?  
A: The use of TELAZOL is contraindicated in in dogs and cats with pancreatic disease. TELAZOL should not be used in dogs and cats with severe cardiac or pulmonary dysfunction.

19) Q: Are there any drugs that should not be used with TELAZOL?  
A: Phenothiazine-derivative drugs should not be used with TELAZOL at dosages indicated for intramuscular (IM) injection because the combination produces respiratory and myocardial depression, hypotension and hypothermia. However, intravenous TELAZOL at a dosage of 2.2-4.4 mg/kg (1-2 mg/lb) has been demonstrated
to be safe in a field study in dogs when used in conjunction with phenothiazine-derivative drugs (acepromazine) administered at dosages from 0.04-0.06 mg/kg IM.

20) Q: Are there specific recommendations for monitoring dogs and cats under TELAZOL anesthesia?
A: As with all anesthetic events, when using TELAZOL for anesthesia, patients should be continuously monitored. Facilities for the maintenance of a patent airway, artificial ventilation and oxygen supplementation should be available. Cats and smaller dogs that have small body mass relative to body surface area should be protected from heat loss during TELAZOL anesthesia. Body temperature should be monitored, and supplemental heat may be required to control hypothermia.

21) Q: What other precautions are listed on the TELAZOL FDA–approved label?
A: The dosage of TELAZOL should be reduced in geriatric animals, those in a debilitated condition or with impaired renal function.
When using TELAZOL as a sole agent, athetoid movement (uncontrolled rhythmic writhing movement) may occur. Athetosis should not be mistaken for lack of anesthesia nor is it indicative of lack of analgesia. Do not give additional anesthesia in an attempt to abolish the athetoid movement. Efforts to eliminate athetoid movement with additional doses of TELAZOL can result in anesthetic overdosage. Additionally, laryngeal, pharyngeal, pinnal, palpebral and pedal reflexes may not be abolished and the animal’s eyes normally remain open with the pupils dilated. The use of a bland ophthalmic ointment is advisable to protect the corneas from desiccation. TELAZOL may not be adequate as the sole anesthetic for surgical procedure. Copious salivation may occur during TELAZOL anesthesia. Atropine (0.02 mg/lb. or 0.04 mg/kg) should be used to control ptyalism.

22) Q: What types of adverse events have been reported with use of TELAZOL?
A: Adverse events reported with TELAZOL administered IM at high dosage > 9.7 mg/kg (4.4 mg/lb) for the cat, and > 6.6 (3 mg/lb) for the dog, include respiratory depression emesis during emergence, excessive salivation, transient apnea, vocalization, erratic recovery and prolonged recovery, excessive tracheal and bronchial secretions when atropine sulfate, was not given before anesthesia, involuntary muscular twitching, hypertonicity, cyanosis, cardiac arrest, pulmonary edema and muscle rigidity during surgical procedures. Central nervous system stimulation and convulsions have also been reported. Tachycardia frequently occurs, particularly in the dog. This rise in heart rate usually lasts about 30 minutes. Either hypertension or hypotension may also occur. Insufficient anesthesia has been reported in dogs. Death has been reported in dogs and cats following TELAZOL administration. Preexisting pulmonary disease, renal disease and shock were causally implicated at necropsy; however, death was drug attributable in at least one dog (of 1072) and one cat (of 1095).

Adverse events reported with TELAZOL administered IV for induction at 2.2 to 4.4 mg/kg (1 to 2 mg/lb.) for the dog, listed in decreasing frequency of occurrence, include post-induction apnea (mean duration of 1 minute), transient hypotension (BP<60 mmHg), hypothermia (<96°F), elevated body temperature (≥ 103°F), low SPO2 (<90 mmHg), nystagmus, emesis, ventricular premature depolarizations, diarrhea, hypersalivation, urticarial, anorexia, hyperthermia, and lethargy.

23) Q: What is the mechanism of action of TELAZOL?
A: TELAZOL has an onset of anesthesia, characterized by analgesia, normal pharyngeal-laryngeal reflexes and cataleptoid anesthesia. TELAZOL produces a state of unconsciousness which has been termed “dissociative” anesthesia in that it appears to selectively interrupt association pathways to the brain before producing somesthetic sensory blockade. Analgesia results from apparent selective interruption of sensory inputs to the brain and usually persists after the anesthetic effect has subsided. Used alone, tiletamine hydrochloride does
not provide adequate muscle relaxation for abdominal surgical procedures. When combined with zolazepam hydrochloride, good muscle relaxation is generally attained during the phase of deep surgical anesthesia.

24) Q: Are there any species differences in anesthetic effects of TELAZOL?
A: When administered at the higher IM dosages, the duration of effect of zolazepam exceeds that of tiletamine in cats so that cats recover with greater degree of tranquilization than anesthetization. In dogs, the duration of effect of tiletamine exceeds that of zolazepam so there is less tranquilization than anesthetization in dogs and the total effect of TELAZOL in dogs is of shorter duration than in cats.

25) Q: What are the cardiovascular and respiratory effects of TELAZOL when administered at the higher IM dosages?
A: In cats, there is a slight lowering of blood pressure during the first hour after injection. Arterial pO2 levels are decreased three minutes after injection but usually return to normal within 15 to 35 minutes. In dogs, a marked, persistent tachycardia occurs within two minutes following TELAZOL IM at 10 mg/kg (4.5 mg/lb). Stroke volume decreases proportionately to the increased heart rate so that cardiac output is maintained. There is an initial increase in systolic blood pressure, with a slight drop in pressure within five minutes. The systolic blood pressure remains decreased throughout the duration of the anesthetic effect, while diastolic pressure increases throughout this same period. At 20 mg/kg (9 mg/lb) IM dosage myocardial depression and decreased cardiac output occurs. During the first 15 minutes after intramuscular administration of TELAZOL, the respiratory rate is doubled while the tidal volume and arterial pO2 levels are decreased with possible hypoxemia and cyanosis. The pulmonary function usually returns to normal within 35 minutes after the administration of TELAZOL.

26) Q: What are the cardiovascular and respiratory effects of TELAZOL when administered IV at 2.2-4.4 mg/kg for induction of anesthesia?
A: The cardiovascular 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. Intubation transiently increased heart rate and/or blood pressure (sympathetic stimulations). Mild to severe respiratory depression was observed after TELAZOL administration and each preanesthetic agent. Adverse reactions were manageable with appropriate care.

27) Q: What are the required storage conditions for TELAZOL?
A: TELAZOL should be stored at controlled room temperature 20° to 25°C (68° to 77°F) prior to use. After initial use, discard unused solution after 7 days when stored at room temperature or after 56 days when kept refrigerated. Only use clear solution. Color of solution may vary from colorless to light amber.

28) Q: Where is TELAZOL manufactured?
A: TELAZOL is made at a Zoetis dedicated facility located in Olot, Spain.

IMPORTANT SAFETY INFORMATION: Do not use TELAZOL in dogs and cats with pancreatic disease, or severe cardiac or pulmonary dysfunction. Do not use for Caesarean section. Safe use in in pregnant dogs or cats has not been established. Use in cats with renal dysfunction is not recommended; pre-existing renal disease may prolong duration of anesthesia. When used for induction of anesthesia, patients should be continuously monitored. Do not use phenothiazine-derivative drugs concomitantly with TELAZOL when given at the IM dosages, as the combination produces respiratory and myocardial depression, hypotension, and hypothermia. Pulmonary edema has been reported in cats. Respiratory depression may occur following administration of high doses of TELAZOL. Post-induction apnea may occur when TELAZOL is administered
IV as an induction agent. Common adverse events included hypotension, hypothermia, elevated body temperature and decreased SPO₂; frequency varied based on the type of premedication used. See full Prescribing Information at https://www.zoetisus.com/locale-assets/pi/telazol_pi.pdf

REFERENCES:

1) TELAZOL (tiletamine and zolazepam for injection) Prescribing Information, NADA 106-111,

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