PREPARATION OF SOLUTION FOR ADMINISTRATION
To each vial add 5 mL sterile water for injection, USP. 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).

Discard unused portion 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 light to dark amber.

CONTRAINDICATIONS
The use of TELAZOL is contraindicated in cats and dogs with pancreatic disease. TELAZOL should not be used in dogs and cats with severe cardiac or pulmonary dysfunction.

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.

WARNINGS
FOR USE IN DOGS AND CATS ONLY:
When using TELAZOL for induction of anesthesia, patients should be continuously monitored. Facilities for the continuous monitoring of cardiac output or respiratory function may be expected to result in prolonged duration of anesthesia.

Pulmonary edema has been reported to occur in cats with the use of TELAZOL. Signs and symptoms include dyspnea, lethargy, anorexia and abnormal behavior. Deaths have been reported occasionally in severely affected individuals. Cats should be observed closely for any signs and symptoms which may suggest respiratory edema. APPROPRIATE THERAPY SHOULD BE INSTITUTED.

The principal route of excretion of both components in the cat is the urine; therefore, TELAZOL is not recommended for use in cats suffering from renal insufficiency.

Balance studies in dogs indicated extensive biotransformation of both components with less than 4% of the dose excreted unchanged in the urine. TELAZOL is excreted predominantly by the kidneys. Preeclamptic renal pathology or impairment of renal function may result in prolonged duration of anesthesia.

Phenothiazine-derivative drugs should not be used with TELAZOL at doses indicated for intramuscular (IM) injection because the combination produces respiratory and myoclonic depression, hypotension and hypothermia.

The safe use of TELAZOL in pregnant animals or on reproduction has not been established. TELAZOL crosses the placental barrier and causes respiratory depression in the neonate.

PRECAUTIONS
The dosage of TELAZOL should be reduced in geriatric dogs and cats, in animals in debilitated condition and in animals with impairment of renal function. Death has occurred in both cats and dogs following intramuscular TELAZOL administration. Premedication with phenothiazine-derivative drugs (acepromazine) administered at dosages from 0.04-0.06 mg/kg IM. Cats and smaller dogs with small body masses in relation to large body surfaces should be protected from heat loss during TELAZOL anesthesia. Body temperature should be monitored, and supplemental heat may be required to control hypothermia. As with other anesthetics, it is prudent to provide for hemostasis during any surgical procedures. Local anesthetics (so as not to obscure any signs of hypothermia). The stimulation of surgical procedures aids in maintaining adequate ventilation. The anesthetized patient must be monitored throughout the procedure, and if cardiopulmonary problems do occur, measures must be taken to assure that no respiratory depression or cardiovascular functions are maintained.

The eyes normally remain open with the pupils dilated. The use of a bland ophthalmic ointment is advisable to protect the cornea from desiccation. The concurrent use of chlorpheniramine will prolong the duration of anesthesia in cats.

Copious salivation may occur during TELAZOL anesthesia. Ptosis may be controlled in dogs and cats by administering atropine sulfate, USP, 0.02 mg/lb (0.04 mg/kg) body weight (IV, IM, or SC) as concurrent medication. Exaggerated swallowing, reflex action and accumulation of saliva may give rise to vomiting and retching.

ADVERSE REACTIONS
For Restraint and Minor Procedures of Short Duration Requires Careful Monitoring
Respiratory depression may occur following administration of high doses of TELAZOL. If at any time respiratory depression becomes excessively depressed and the animal becomes cyanotic, resuscitative measures should be instituted promptly. Adequate pulmonary ventilation using either oxygen or room air is recommended as a resuscitative measure.

Adverse reactions reported include emesis during emergence, excessive salivation, transient ataxia, vocalization, erratic recovery and prolonged recovery, excessive tracheal and bronchial secretions when atropine sulfate was used, ataxia, incoordination, involuntary muscular twitching, hyperactivity, 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 5-10 minutes. Either death or hyperthermia may also occur. Insufficient anesthesia has been reported in dogs. Death has been reported in dogs and cats following TELAZOL administration.

Intravenous Induction of Anesthesia Followed by Maintenance with Inhalant Anesthetics
In a field study to assess the effectiveness and safety of TELAZOL administered intravenously at 1-2 mg/lb (2.2-4.4 mg/kg) for the induction of anesthesia followed by maintenance with inhalant anesthesia in dogs, 144 dogs were intravenously administered TELAZOL (See Effectiveness). Sixteen adverse reactions occurred during the study: nystagmus (5), emesis (4), diarrhea (2), and one occurrence each of hypersalivation, urticarial, anorexia, hyperthermia, and lethargy. All adverse reactions resolved by the end of the study.

Pharmacological side effects were generally related to the TELAZOL and did not result in adverse effects.

Post-induction apnea (time from induction to first inspiration ≥30 seconds) was observed in 49.3% of dogs across all treatment groups with a mean duration of one minute. The highest overall frequency and duration of post-induction apnea was in the alpha2-agonist + opioid groups.

Overall, 36 dogs received assisted ventilation. Assisted ventilation was needed most frequently in the alpha2-agonist + opioid group (at procedure start, possibly after an apneic period) then decreased in frequency as the procedure continued. Sixteen dogs experienced oxygen saturation (SpO2) ≤90 mmHg; 7 in the alpha2-agonist + opioid groups, 6 in the phenothiazine + opioid groups, and 3 in the opioid alone groups. Twenty-five dogs had a temperature ≥103°F during the study, with 12 of these occurring prior to preanesthetic administration only. Of the remaining 13 dogs, 7 were in the alpha2-agonist + opioid groups, 5 were in the...
opioid alone groups, and 1 in the phenothiazine + opioid groups. One dog was reported with hyperthermia as an adverse reaction in the alpha-agonist + opioid treatment groups. The dog became excitable during recovery and its temperature elevated to 105.7°F. Hyperthermia resolved with treatment of IV fluids and cooling.

Twenty-six dogs experienced temperatures ≥9°F at one or more timepoints. Most dogs received supplemental heat during surgery.

Fifty-nine dogs had mean blood pressure (BP) values ≤50 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.

Venetian hemodynamic profiles in 3 dogs in the alpha-agonist + opioid group. This transient rhythm disturbance is not uncommon in dogs receiving alpha-agonists or inhalant anesthetics. One dog in the phenothiazine + opioid group showed transient ST depression that could have been due to cardiac hypoxia. All dogs recovered normally.

For a copy of the Safety Data Sheet (SDS) or to report adverse effects call Zoetics Inc. at 1-888-963-8471. Additional information can be found at ZoetisUS.com.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/AnimalVeterinary/SafetyHealth.

CLINICAL PHARMACOLOGY

Mechanism of Action

TELAZOL is a rapid-onset, short-acting combination of tiletamine hydrochloride and zolazepam hydrochloride. Tiletamine hydrochloride is a dissociative anesthetic agent whose pharmacologic action is characterized by profound analgesia, normal pharyngeal-laryngeal reflexes and cataleptoid anesthesia. The anesthetic state produced does not fit into the conventional classification of stages of anesthesia, but instead 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. Cranial nerve and spinal reflexes remain active; however, these reflexes must not be confused with inadequate anesthesia. Analgesia results from apparent selective interruption of sensory inputs to the brain and usually persists after the anesthetic effect has subsided.

Protective reflexes, such as coughing and swallowing, are maintained under tiletamine anesthesia. Other reflexes, e.g., corneal, pedal, are maintained during tiletamine anesthesia, and should not be used as criteria for judging depth of anesthesia. The eyes normally remain open with the pupil dilated. It is suggested that a bimaxillary incision may be performed under tiletamine anesthesia. 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.

Pharmacokinetics

The pharmacokinetics of TELAZOL Injectable solution was evaluated in 12 healthy adult Beagle dogs, following a single intravenous (IV) administration of 2.2 mg/kg bodyweight, which is equivalent to 1.1 mg/kg for both tiletamine hydrochloride and zolazepam hydrochloride. After administration of 2.2 mg/kg TELAZOL IV, the initial mean plasma concentration (C0) was 1018 ng/mL. C0 was 6223 ng/kg/h and the area under the curve to the last measured concentration (AUC 0-last) was 178 ng*hr/mL, and steady state volume of distribution (Vss) was 3250 mL/kg. The mean elimination half-life of tiletamine was 0.87 hours.

For zolazepam, the mean C0 was 2594 ng/mL, CL was 1993 mL/kg/h and Vss was 604 mL/kg. The mean elimination half-life of tiletamine was 0.41 hours. The mean C0 and AUC were approximately 2.5 and 3 times, respectively, greater for zolazepam than for tiletamine. However, the mean half-life of zolazepam at 0.87 hours. In dogs, the duration of effect of tiletamine exceeds that of zolazepam so there is a lesser degree of tranquilization than anesthetization. There is a slight lowering of blood pressure during the first 15 minutes after intramuscular administration of 9 mg/lb (20 mg/kg) of TELAZOL, the respiratory rate is reduced while the tidal volume is decreased to less than one-half of control values. Arterial pO2 levels also decrease. This may be evidenced by hypoxemia and cyanosis. The pulmonary function usually returns to normal within 35 minutes after the administration of TELAZOL.

Preanesthetic Care

Six healthy Beagle dogs (3 males and 3 females), at least 8 months of age, in ranging in body weight between 5.6 and 9.4 kg, were fitted with a telemetry device that captured systemic arterial blood pressures, heart rates, and other physiologic parameters during the anesthetic period. Each dog received a total of 6 treatments with at least a 7-day washout between periods. During each period, dogs received 1 of the following 6 preanesthetics prior to the TELAZOL administration: placebo (0.9% saline), acetylcholine low dose (0.1 mg/kg body weight [BW]), acetylcholine high dose (1.1 mg/kg BW), desmopressin low dose (125 mcg/kg body surface area [BSA]), desmopressin high dose (375 mcg/m2 BSA), or butorphanol (0.4 mcg/kg BW). Blood samples were collected at intubation, end of isoflurane administration, and after anesthesia when the dogs were able to walk. Plasma concentrations of tiletamine and zolazepam were measured using a validated method. Preanesthetic treatment with high dose acetylcholine and both high and low doses of desmopressin resulted in substantial increases in plasma concentrations of tiletamine and zolazepam at intubation. The increase in the tiletamine plasma concentrations was approximately 2X higher for the high dose of acetylcholine and 2.7 to 4.5X higher for the low and high doses of desmopressin, respectively, compared to saline. The increase in zolazepam plasma concentrations was 1.5X higher for the high dose acetylcholine, and 1.8 to 2.8X higher for the low and high doses of desmopressin, respectively, compared to saline.

No information on the dose-sparing of TELAZOL was obtained during the study because the dogs were given the full initial half-dose (2.2 mg/kg) and not actually administered TELAZOL ‘to effect’. The average total dose of test article administered to the dogs was 2.6 mg/kg for the saline group and 2.2 mg/kg for the other treatment groups. One dog (saline group) required more than the initial 2.2 mg/kg bolus to achieve intubation at the first attempt.

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 desmopressin 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 groups.

All dogs in all treatment groups achieved successful anesthetic plane following TELAZOL administration and were intubated and induced to isoflurane anesthesia uneventfully. The quality of intubation, and occurrence and severity of adverse effects (e.g., apnea and bradycardia) following TELAZOL administration and intubation revealed differences among preanesthetic treatment groups. The Cardiovascular and respiratory changes observed in dogs receiving high and low preanesthetics. Medication used in combination with TELAZOL. Acetylcholine and isoflurane administration decreased arterial blood pressure. Desmopressin 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 managed using appropriate supportive care.

STORAGE CONDITIONS

Store at controlled room temperature 20° to 25°C (68° to 77°F). 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.

HOW SUPPLIED

TELAZOL (tiletamine and zolazepam for injection) is available in individual vials of 5 mL solution when reconstituted. The addition of 5 mL diluent produces a solution containing the equivalent of 50 mg tiletamine base, 50 mg zolazepam base and 5.77 mg mannitol per milliliter.

10 mL vial -100 mL total (equivalent to 50 mg tiletamine and 50 mg zolazepam) when reconstituted Approved by FDA under NADA # 106-111

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ANIMAL SAFETY

TELAZOL has a wider margin of safety in cats than in dogs. Dogs have survived repeated IM dosage regimens of 13.6 mg/kg (30 mcg/kg) (maximum safe dose) for eight successive days. This is approximately two times the maximum recommended therapeutic dose. Cats have survived IM dosage regimens of up to 32.7 mg/kg (72 mg/kg) (maximum safe dose) on alternate days for seven sessions. This is 4.6 times the maximum recommended therapeutic dose. However, these regimens do not obviate prudent anesthetic practices. Some degree of tolerance has been reported. This tolerance appears to be species-variable.

Cats

In the, the duration of effect of zolazepam exceeds that of tiletamine so that as the animal recovers there is a greater degree of tranquilization than anesthetization. There is a slight lowering of blood pressure during the first hour after injection. Heart rate and electrocardiogram readings are unaffected by TELAZOL tiletamine and zolazepam for injection). Arterial pO2 levels are decreased three minutes after injection but usually return to normal within 15 to 30 minutes.

Dogs

In dogs, the duration of effect of tiletamine exceeds that of zolazepam so there is a lesser degree of tranquilization than anesthetization in this species. The total effect of TELAZOL in dogs is of shorter duration than in cats.