SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZOLETIL 100 (50 mg/ml+50 mg/ml) Lyophilisate and Solvent for Solution for Injection for Dogs and Cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of 970 mg lyophilisate contains:

Active substances :	
Tiletamine (as hydrochloride)	250.00 mg
Zolazepam (as hydrochloride)	250.00 mg

Each vial of 5 ml solvent contains:

Water for injections	5.00 ml

Each ml of reconstituted solution contains:

Active substances:	
Tiletamine (as hydrochloride)	50.00 mg
Zolazepam (as hydrochloride) ……..	50.00 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate and solvent for solution for injection.

Appearance of the lyophilisate: White to slightly yellow compact mass;
Appearance of the solvent: Clear colourless liquid;
Appearance of the reconstituted solution: Clear, colourless to slightly green-yellow solution, free from particles.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs and cats.

4.2 Indications for use, specifying the target species

General anaesthesia.

4.3 Contraindications

Do not use in cases of hypersensitivity to the active substances or to any of the excipients.
Do not use in animals with severe cardiac or respiratory disease, or in animals with renal, pancreatic or hepatic insufficiency.
[illegible] event of severe hypertension.

Do not use in rabbits.
Do not use in animals with head trauma or intracranial tumours.
Do not use for caesarean section.
Do not use in pregnant bitches and queens.

4.4 Special warnings for each target species

In dogs, since zolazepam is eliminated more quickly than tiletamine, there is a shorter duration of tranquilisation than there is of anaesthesia.

4.5 Special precautions for use

i) Special precautions for use in animals

Animals should be fasted for 12 hours prior to anaesthesia.
Remove anti-parasite collar 24 hours before anaesthesia.
If necessary, hypersalivation can be controlled with the administration of anticholinergic agents, such as atropine, before the anaesthesia according to the benefit/risk assessment by the responsible veterinarian.
Please refer to section "Interaction with other medicinal products and other forms of interaction" in case of the use of pre-anaesthetic agents.
Keep anaesthetised animals away from excessive noise and visual stimuli.

Apneustic breathing may be observed more commonly in cats after intravenous injection than after intramuscular injection. Especially for high dosages, such abnormal breathing patterns last for up to 15 minutes and then breathing returns to normal. In case of prolonged apnea respiratory assistance should be provided.
Close observation of dogs during the first 5-10 minutes after induction is recommended especially in animals with cardiopulmonary disease.

The product may cause hypothermia, in susceptible animals (small body surface area, low ambient temperature) supplemental heat should be applied if needed.
In dogs and cats the eyes remain open after receiving the product and should be protected from injury and excessive drying of the cornea.
Dosage may need to be reduced in geriatric or debilitated animals, or in animals with renal dysfunction.
Reflexes (e.g. palpebral, pedal, laryngeal) are not abolished during anaesthesia and therefore use of this product alone may not be adequate if surgery is performed on these areas.

Redosing may prolong and worsen recovery.
In the event of reinjections, side effects (hyper-reflexia, neurological problems) can be produced due to tiletamine. It is recommended that the recovery phase occurs in a calm environment.

ii) Special precautions to be taken by the person administering the veterinary medicinal product to animals

In case of accidental self-injection seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive due to risk of sedation.
Wash splashes from skin and eyes immediately. In case of eye irritation, seek medical advice.
Wash hands after use.

This product may cross the placenta and be harmful to the foetus, therefore women who are pregnant, or are suspected to be pregnant, should not use the product.

4.6 Adverse reactions (frequency and seriousness)

Pain upon injection has been reported very rarely. This is most prevalent in cats.
The following signs have been reported very rarely, mainly during the awakening phase in the dog, and during surgery and the awakening phase in the cat;

- Neurological signs – prostration, convulsions, coma.
- Cardio-respiratory signs – dyspnoea, tachypnoea, bradypnoea, tachycardia, cyanosis, have been noted at doses of 20 mg/kg and above.
- Certain systemic signs – hypothermia, hyperthermia, pupillary disorder, hypersalivation, hypersensitivity to external stimuli, agitation, vocalisation.

Prolonged anaesthesia and difficulties when awakening (with myoclonus, restlessness, ataxia, paresis, etc.) have been observed in the recovery phase.
All reactions are reversible and disappear once the active substance is eliminated from the body.

The frequency of adverse reactions is defined using the following convention:
- very common (more than 1 in 10 animals treated displaying adverse reaction(s))
- common (more than 1 but less than 10 animals in 100 animals treated)
- uncommon (more than 1 but less than 10 animals in 1,000 animals treated)
- rare (more than 1 but less than 10 animals in 10,000 animals treated)
- very rare (less than 1 animal in 10,000 animals treated, including isolated reports).

4.7 Use during pregnancy, lactation or lay

Laboratory studies in laboratory animals have not produced any evidence of teratogenic effects.

The product crosses the placenta and may cause respiratory depression in newborns that can be fatal for puppies and kittens. The safety of the veterinary medicinal product has not been established during pregnancy or lactation. Do not use during pregnancy. During lactation, use only according to the benefit-risk assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

The benefit-risk assessment for using the product with other pre-anaesthetic or anaesthetic agents must take into consideration the dosages of the agents used, the nature of the intervention and the ASA (American Society of Anaesthesiologists) class to which the animal belongs. The required dosage of tiletamine-zolazepam is likely to change depending on which agents are concurrently used.
The dosage of tiletamine – zolazepam may need to be reduced when used concomitantly with pre-anaesthetic and other anaesthetic agents. Premedication with phenothiazine tranquilisers (e.g. acepromazine) can cause increased cardio-respiratory depression and an increased hypothermic effect that occurs in the last phase of anaesthesia.
Do not use medications containing chloramphenicol during the pre- or intra-operative period, as this slows down elimination of the anaesthetics.

4.9 Amounts to be administered and administration route

Intramuscular or intravenous use.

Dosage:
The content of the lyophilisate vial is to be diluted in 5 ml of the attached solvent.
The dosage is expressed in mg of the product, on the understanding that the reconstituted product is at a concentration of 100 mg per ml and contains 50 mg of tiletamine per ml and 50 mg of zolazepam per ml.

When the product is administered intramuscularly (unable to stand in 3 to 6 minutes) or intravenously (unable to stand in less than one minute), the recommended therapeutic dosages are the following:

IN DOGS	Intramuscular route	Intravenous route
Tests and procedures causing little pain	7 to 10 mg/kg bw 0.07 to 0.1 mL/kg bw	5 mg/kg bw 0.05 mL/kg bw
Minor surgical procedures, anaesthesia of short duration	10 to 15 mg/kg bw 0.1 to 0.15 mL/kg bw	7.5 mg/kg bw 0.075 mL/kg bw
Painful interventions	15 to 25 mg/kg bw 0.15 to 0.25 mL/kg bw	10 mg/kg bw 0.1 mL/kg bw

IN CATS	Intramuscular route	Intravenous route
Tests and procedures causing little pain	10 mg/kg bw 0.1 mL/kg bw	5 mg/kg bw 0.05 mL/kg bw
Orthopaedic operation	15 mg/kg bw 0.15 mL/kg bw	7.5 mg/kg bw 0.075 mL/kg bw

Please refer also to sections “Adverse reactions” and/or “Overdose” since adverse reaction might occur at therapeutic doses.
Intravenous injections to be repeated, if needed, at between 1/3 and 1/2 of the initial dose but the total dosage should not exceed 26.4 mg/kg bw (0.264 mL/kg bw).

The individual response to Tiletamine-Zolazepam will vary depending upon several factors. Therefore, the dosage should be adjusted, at the discretion of the practitioner, based on the species, the type and duration of surgical procedure, the other concomitant medication (pre-anaesthetic and other anaesthetic agents) and the health status of the animal (age, obesity, severe organic deficiencies, state of shock, debilitating diseases).

Duration of anaesthesia: 20 to 60 minutes depending on dose.

The product should not be used as sole anaesthetic agent for painful operations. For these operations the product should be combined with an appropriate analgesic.

Pre-surgical preparation:
As for all anaesthetics animals should be fasted for at least 12 hours before anaesthesia.
In dogs and cats, the use of atropine subcutaneously, 15 minutes before injection, may be considered.

Recovery period:
Analgesia lasts longer than surgical anaesthesia. Return to normal is progressive and can last 2 to 6 hours in a calm environment (avoid excessive noise and light). Recovery may be delayed due to an overdose in obese, old or debilitated animals.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

100 mg per kg constitutes a lethal dose for cats and dogs when administered intramuscularly, i.e., 5 to 10 times the anaesthetic dose. In the event of an overdose and in obese or old animals, recovery may be slower.

Overdosed animals must be monitored carefully. The signs of overdosage are mainly cardio-respiratory depression that can appear from 20 mg/kg depending on the animal's health, the level of central nervous system depression, and whether hypothermia is present. An earlier warning sign of overdosage is the loss of cranial and spinal reflexes. Prolongation of anaesthesia can be produced.

There is no specific antidote and treatment is symptomatic. Doxapram may have antagonistic activity against the tiletamine-zolazepam, increasing both heart and respiratory rates and reducing the arousal time.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Medication for the nervous system, other general anaesthetics, combinations.

ATC vet-code: QN01AX99.

5.1 Pharmacodynamic properties

Tiletamine is a compound belonging to the family of phencyclidines and is pharmacologically similar to ketamine. It antagonises NMDA-type receptors (N-methyl-D-aspartate) of the excitatory neurotransmitter, glutamic acid. It generates a so-called dissociative anaesthesia because it depresses certain cerebral regions such as the thalamus and the cortex whilst other regions, in particular the limbic system, remain active.
Zolazepam is a benzodiazepine and pharmacologically similar to diazepam. It has a sedative, anxiolytic and muscle-relaxing action.

Associations in proportions of 1/1 of two compounds with complementary actions enable the following effects:
- fast catalepsy, without agitation, followed by relaxation of the muscle,
- moderate superficial, immediate and visceral analgesia,
- surgical anaesthesia with muscle relaxation, preservation of laryngeal, pharyngeal and palpebral reflexes, without bulbar depression.

5.2 Pharmacokinetic particulars

After intramuscular administration of 10 mg of tiletamine per kg and 10 mg of zolazepam per kg, the peak plasma concentrations of tiletamine and zolazepam (Cmax) are reached within 30 minutes in dogs and cats, indicating fast absorption.
The terminal half-life of tiletamine ($T_{1/2}$) is 2.5 hours in cats. It is shorter in dogs (1.2 to 1.3 hour).
The terminal half-life of zolazepam is longer in cats (4.5hours) than in dogs (< 1 hour).
Both active substances are extensively metabolised. Less than 4% of the dose is found in a non-metabolised form in urine and less than 0.3% in faeces.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilisate vial
Sodium sulfate, anhydrous
Lactose monohydrate

Solvent vial
Water for injections

6.2 Major Incompatabilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

6.3 Shelf life

Shelf life of the lyophilisate as packaged for sale: 2 years.
Shelf life of the solvent as packaged for sale: 3 years.
Shelf life after reconstitution according to directions: 24 hours between 2°C and 8°C

6.4 Special precautions for storage

Keep the vials in the outer carton in order to protect from light.
After reconstitution, store in a refrigerator (2°C - 8°C).

6.5 Nature and composition of immediate packaging

Lyophilisate:
Colourless Type 1 glass vial
Bromobutyle rubber stopper
Aluminium cap

Solvent:
Colourless Type 1 glass vial
Chlorobutyle rubber stopper
Aluminium cap

Pack size:
1 vial of 270 mg lyophilisate and 1 vial of 5 ml solvent

10 vials of 970 mg lyophilisate and 10 vials of 5 ml solvent

Not all pack sizes may be marketed.

6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products

Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Virbac
Premiere Avenue
2065M-L I D
06516 Carros Cedex
France

8. MARKETING AUTHORISATION NUMBER

Vm 05653/4194

9. DATE OF FIRST AUTHORISATION

20 April 2016

10. DATE OF REVISION OF THE TEXT

December 2020

Approved 23 December 2020