ANNEX III

LABELLING AND PACKAGE LEFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Box containing 1 or 10 vials of lyophilisate and 1 or 10 vials of solvent

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZOLETIL 50 (25 mg/ml+25 mg/ml) lyophilisate and solvent for solution for injection for dogs and cats (FR / NL / PL / IE / MT)

ZOLETIL 50 VET 25 mg/ml+25 mg/ml lyophilisate and solvent for solution for injection for dogs and cats (SE / FI)

Tiletamine, Zolazepam

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml of reconstituted solution contains:
Tiletamine (as hydrochloride)……..25.00 mg
Zolazepam (as hydrochloride)……..25.00 mg

3. PHARMACEUTICAL FORM

Lyophilisate and solvent for solution for injection.

4. PACKAGE SIZE

1 vial of 675 mg lyophilisate and 1 vial of 5 ml solvent
10 vials of 675 mg lyophilisate and 10 vials of 5 ml solvent

5. TARGET SPECIES

Dogs and cats

6. INDICATION(S)

General anaesthesia

7. METHOD AND ROUTE(S) OF ADMINISTRATION

Intramuscular or intravenous use.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Accidental injection is dangerous - read the package leaflet before use. Due to the risk, women who are pregnant or are suspected to be pregnant should not use the product.

10. EXPIRY DATE

<EXP {month/year}>
Shelf life after reconstitution: 7 days.
Once reconstituted, use by: …….

11. SPECIAL STORAGE CONDITIONS

Keep the vials in the outer carton in order to protect from light.
After reconstitution, store in a refrigerator.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read the package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only.

14. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

VIRBAC
1ère avenue 2065 m L.I.D
06516 Carros cedex
FRANCE

16. MARKETING AUTHORISATION NUMBER(S)

17. MANUFACTURER'S BATCH NUMBER

<Batch><Lot> {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial of lyophilisate

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZOLETIL 50 (25 mg/ml+25 mg/ml) lyophilisate for solution for injection for dogs and cats (FR / NL / PL / IE / MT)

ZOLETIL 50 VET 25 mg/ml+25 mg/ml lyophilisate for solution for injection for dogs and cats (SE / FI)

Tiletamine, Zolazepam

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

After reconstitution in 5 ml solvent: 25 mg tiletamine and 25 mg zolazepam per ml.

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

675 mg

4. ROUTE(S) OF ADMINISTRATION

IV or IM

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

<Batch><Lot> {number}

7. EXPIRY DATE

<EXP {month/year}>
Shelf life after reconstitution: 7 days.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Vial of solvent

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZOLETIL 50 (25 mg/ml+25 mg/ml) solvent for solution for injection for dogs and cats (FR / NL / PL / IE / MT)

ZOLETIL 50 VET 25 mg/ml+25 mg/ml solvent for solution for injection for dogs and cats (SE / FI)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

5 ml

4. ROUTE(S) OF ADMINISTRATION

IV or IM

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

<Batch><Lot> {number}

7. EXPIRY DATE

<EXP {month/year}>

8. THE WORDS “FOR ANIMAL TREATMENT ONLY”

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET:

ZOLETIL 50 (25 mg/ml+25 mg/ml) lyophilisate and solvent for solution for injection for dogs and cats (FR / NL / PL / IE / MT)

ZOLETIL 50 VET 25 mg/ml+25 mg/ml lyophilisate and solvent for solution for injection for dogs and cats (SE / FI)

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder and manufacturer responsible for batch release:
VIRBAC – 1ère avenue 2065 m LID – 06516 Carros cedex - FRANCE

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

ZOLETIL 50 (25 mg/ml+25 mg/ml) lyophilisate and solvent for solution for injection for dogs and cats (FR / NL / PL / IE / MT)

ZOLETIL 50 VET 25 mg/ml+25 mg/ml lyophilisate and solvent for solution for injection for dogs and cats (SE / FI)

Tiletamine, Zolazepam

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

Each vial of 675 mg lyophilisate contains:
Active substances:
Tiletamine (as hydrochloride)..... 125.00 mg
Zolazepam (as hydrochloride)..... 125.00 mg

Each vial of 5 ml solvent contains:
Benzyl alcohol (E1519)..... 0.100 g
Water for injections..... 5.00 ml

Each ml of reconstituted solution contains:
Active substances:
Tiletamine (as hydrochloride)..... 25.00 mg
Zolazepam (as hydrochloride) …….25.00 mg
Excipient:
Benzyl alcohol (E1519) …….20.00 mg

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. INDICATION(S)

General anaesthesia

5. 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.
Do not use in the 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.

6. ADVERSE REACTIONS

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 in 10,000 animals treated, including isolated reports).

If you notice any side effects, even those not already listed in this package leaflet or if you think that the medicine has not worked, please inform your veterinary surgeon.

Alternatively you can report via your national reporting system {national system details}.

7. TARGET SPECIES

Dogs and cats.

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

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 50 mg per ml and contains 25 mg of tiletamine per ml and 25 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 0.14 to 0.2 mL/kg bw	5 mg/kg bw 0.1 mL/kg bw
Minor surgical procedures, anaesthesia of short duration	10 to 15 mg/kg bw 0.2 to 0.3 mL/kg bw	7.5 mg/kg bw 0.15 mL/kg bw

Painful interventions	15 to 25 mg/kg bw 0.3 to 0.5 mL/kg bw	10 mg/kg bw 0.2 mL/kg bw

IN CATS	Intramuscular route	Intravenous route
Tests and procedures causing little pain	10 mg/kg bw 0.2 mL/kg bw	5 mg/kg bw 0.1 mL/kg bw
Orthopaedic operation	15 mg/kg bw 0.3 mL/kg bw	7.5 mg/kg bw 0.15 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 (0.53 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.

9. ADVICE ON CORRECT ADMINISTRATION

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.

10. WITHDRAWAL PERIOD(S)

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Keep out of the sight and reach of children.

Keep the vials in the outer carton in order to protect from light.
After reconstitution, store in a refrigerator (2 °C – 8 °C).
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and vial label after “EXP”. The expiry date refers to the last day of that month.

Shelf life after reconstitution according to directions: 7 days between 2°C and 8°C.
Once reconstituted, using the in-use shelf-life which is specified on this package leaflet, the date on which any product remaining in the container should be discarded, should be determined. This discard date should be written in the space provided.

12. SPECIAL WARNING(S)

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.

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 occur in a calm environment.

The product contains benzyl alcohol, which has been documented to cause adverse reactions in neonates. Therefore, the use of the veterinary medicinal product is not recommended in very young animals.

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.
Benzyl alcohol may cause hypersensitivity (allergic) reactions. People with known hypersensitivity to benzyl alcohol should avoid contact with the product.

Pregnancy and lactation:
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 yet 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.

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.

Overdose (symptoms, emergency procedures, antidotes):
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.

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

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

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

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

MM/YYYY

15. OTHER INFORMATION

Pack size:
1 vial of 675 mg lyophilisate and 1 vial of 5 ml solvent
10 vials of 675 mg lyophilisate and 10 vials of 5 ml solvent

Not all pack sizes may be marketed.

For animal treatment only