ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LEISGUARD 5 mg/ml Oral Suspension for Dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:
Domperidone 5 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Methyl parahydroxybenzoate (E218)	1.80 mg
Propyl parahydroxybenzoate	0.20 mg
Quinoline yellow (E104)	0.20 mg
Sorbitol, liquid (non crystallising)	
Microcrystalline cellulose and carmellose sodium	
Saccharin sodium	
Polysorbate 20	
Sodium hydroxide	
Water, purified	

Yellow suspension

3. CLINICAL INFORMATION

3.1. Target species

Dogs

3.2. Indications for use for each target species

To reduce the risk of developing an active infection and clinical disease in case of contact with *Leishmania infantum*, through the enhancement of the cell-mediated immune response.

The efficacy of the veterinary medicinal product has been demonstrated in dogs under multiple natural parasite exposure in zones with high infection pressure.

Control of clinical progression of canine leishmaniosis at early stages of the disease (dogs with low to moderate positive antibody levels and mild clinical signs such as peripheral lymphadenopathy or papular dermatitis).

3.3. Contraindications

Do not use whenever stimulation of gastric motility might be dangerous eg. In the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with prolactin-secreting pituitary tumor.
Domperidone is metabolized by the liver, therefore it should not be administered to patients with liver failure.

3.4. Special warnings

In case of severe infections, adequate aetiological treatment should be established in order to lower the parasitic load prior to consider a treatment with this veterinary medicinal product. In all cases, and taking into account the highly variable evolution of the disease, close patient follow up is recommended in order to adapt the treatment to the clinical stage of the animal, as required.

3.5. Special precautions for use

Special precautions for safe use in the target species:

Administration of this veterinary medicinal product produces a transitory increase in plasma prolactin and could induce endocrine disturbances such as galactorrhoea. Therefore it should be used with caution in animals with previous episodes of pseudopregnancy.

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

People with known hypersensitivity to domperidone or to any of the excipients should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.Do not smoke, eat or drink while handling the product.

Special precautions for the protection of the environment:

Not applicable.

3.6. Adverse events

Dogs:

Rare (1 to 10 animals / 10,000 animals treated):	Mammary gland disorders (mammary hyperplasia and milk production increase)[1] Apathy[2], Appetite loss[2] Abdominal pain, Diarrhoea, Emesis
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Behavioural disorders

[1]This is considered a consequence of the prolactine peaks induced by domperidone, which disappear after treatment discontinuation.

[2]These signs disappear once the treatment is withdrawn.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7. Use during pregnancy, lactation or lay

Pregnancy:

Laboratory studys in laboratory animals have not produced any evidence of teratogenic or foetotoxic effects. Signs of maternal toxicity were not seen in laboratory animals at doses 20 times higher than the recommended dose. However, there are no adequate and well controlled studies in pregnant bitches; therefore use only in accordance with the benefit/risk assessment by the responsible veterinarian.

Lactation**:**
Administration of domperidone to lactating females of several species has been shown to induce an increase of milk production. Administration of the veterinary medicinal product to lactating bitches is likely to induce the same effect.

3.8. Interaction with other medicinal products and other forms of interaction

Cabergoline is a dopamine agonist that inhibits prolactin release from the pituitary gland. Therefore, its effects are antagonistic to those of domperidone.
Do not administer with stomach antacids such as omeprazole, cimetidine, or antacids
Domperidone should not be used with dopaminergic drugs such as dopamine or dobutamine

3.9. Administration routes and dosage

0.5 mg/kg/d, equivalent to 1 ml/10 kg of Leisguard, once daily, during 4 consecutive weeks.

The veterinary medicinal product may be administered directly into the mouth or mixed with food. To ensure a correct dosage, body weight should be determined as accurately as possible

Shake well before use.

There are several schedules of dosing:

A) for reducing the risk of developing an active infection and clinical disease in case of contact with Leishmania infantum,

In seronegative animals that have never showed any sign of *Leishmania spp.* infection, but live or travel to an endemic area, domperidone treatments should be programmed, taking into account the temporary prevalence of leishmaniosis vectors *(Phlebotomus spp.)* in the geographic area of the patient location or destination.

In high prevalence areas or in climates with a long infective season, one treatment every four months should be administered. In the Mediterranean area, it would be advised to treat in June, October and February.
In low prevalence areas, one treatment period at the beginning of the infective season and another treatment shortly after the end may suffice.

In all cases, the treatment strategy must be established by the attending veterinarian in accordance with the local incidence of the disease and temporary presence of the infective vectors.

B) For the Control of clinical progression of canine leishmaniosis at early stages of the disease

The treatment should be started immediately after diagnosis in order to help animals to self-limit the disease.

Treatment with the veterinary medicinal product may be repeated as needed, in accordance with the clinical and serological follow up performed by the attending veterinarian.

3.10. Symptoms of overdose (and where applicable, emergency procedures andantidotes)

In tolerance trials performed in dogs, this veterinary medicinal product has been administered at five times the recommended doses during periods up to one year with no noticeable adverse events.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

Administration conditions: To be administered by a veterinary surgeon or under their direct responsibility.

3.12. Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:
ATCvet Code: QP51DX06

4.2. Pharmacodynamics

Domperidone is a dopamine antagonist that promotes the release of prolactin from the pituitary gland. Its repeated daily administration results in daily regular acute and reversible peaks in prolactin blood levels with stimulatory effects on the cellular immune system, leading to activation of phagocytic leukocytes and as a result, to efficient intracellular microorganism (*Leishmania spp.*) reduction, at "in vitro" conditions. Domperidone also has anti-emetic and gastrokinetic properties due to its antagonism of dopamine receptors.

4.3. Pharmacokinetics

Absorption

In fasting dogs, domperidone is rapidly absorbed reaching peak plasma concentrations (Cmax) of 16.6 ng/mL at 2 hours after oral administration. Oral absolute bioavailability of domperidone is low (24%) due to an extensive first-pass metabolism in the gut wall and liver. Domperidone's bioavailability is not affected when taken with food.

In studies performed in dogs at oral dosages between 2.5 and 40 mg/kg domperidone does not accumulate or induce its own metabolism. Domperidone is 91-93% bound to plasma proteins.

Distribution

Distribution studies with radiolabelled drug in animals have shown wide tissue distribution, although it does not readily cross the blood-brain barrier. Small amounts of drug cross the placenta in rats.

Metabolism

Domperidone undergoes rapid and extensive hepatic metabolism by hydroxylation and N-dealkylation. Aromatic hydroxylation of domperidone yields (hydroxy-domperidone) which is the main metabolite found in faeces. N-dealkylated metabolites and their conjugates can be detected in urine. None of the identified metabolites has any pharmacological activity.

Excretion

Elimination half-life (T1/2) is of 3.2 h. The distribution volume (Vd) of 3.3 L/kg, and plasma clearance (Cl) of 0.73 L/h/kg. The proportion of the drug excreted unchanged is small (15% of faecal excretion and approximately 2% of urinary excretion). The amount excreted in faeces or urine corresponds to 60% and 28% of the oral dose respectively. Very small amounts may be found in milk.

5. PHARMACEUTICAL PARTICULARS

5.1. Major incompatibilities

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

5.2. Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 4 years
Shelf-life after first opening the immediate packaging: 8 months

5.3. Special precautions for storage

Store in the original package.
Protect from light.

5.4. Nature and composition of immediate packaging

A 60 ml high-density polyethylene (HDPE) bottle closed with a low density polyethylene (LDPE) adapter and a HDPE child-proof screw-cap. The medicinal product is supplied with two syringes (LDPE barrel, polystyrene (PS) plunger and LDPE piston), one graduated up to 1.5 ml and the other graduated up to 5 ml.

DIVASA-FARMAVIC, S.A.:

Package sizes:
Carton box with 1 bottle of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 2 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 3 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 4 bottles of 60 ml and 2 syringes of 1.5 and 5 ml

SINCROFARM, S.L.:

Package sizes:
Carton box with 2 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 3 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 4 bottles of 60 ml and 2 syringes of 1.5 and 5 ml

Not all pack sizes may be marketed.

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

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Ecuphar Veterinaria S.L.U.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

Box with bottles of 60 ml

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LEISGUARD 5 mg/ml Oral Suspension for Dogs

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Domperidone 5 mg

3. PACKAGE SIZE

60 ml
2x60 ml
3x60 ml
4x60 ml

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral suspension

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp {mm/yyyy}
Once opened use within 8 months
Use by…

9. SPECIAL STORAGE CONDITIONS

Store in the original package.
Protect from light.

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

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

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Ecuphar
An Animalcare Company

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

Label of bottle

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LEISGUARD 5 mg/ml Oral Suspension for Dogs

2. STATEMENT OF ACTIVE SUBSTANCES

Each ml contains:
Domperidone 5 mg

3. TARGET SPECIES

Dogs

4. ROUTES OF ADMINISTRATION

Read the package leaflet before use.

5. WITHDRAWAL PERIODS

6. EXPIRY DATE

Exp {mm/yyyy}
Once opened use within 8 months
Use by…

7. SPECIAL STORAGE PRECAUTIONS

Store in the original package.
Protect from light.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Ecuphar
An Animalcare Company

9. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Label of bottle

Reduce immediate labelling text in the artworks to be used only when space problems occur when combining several languages in the same pack.

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

LEISGUARD 5 mg/ml Oral Suspension for Dogs

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Domperidone 5 mg/ml

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp {mM/yyyy}

B. PACKAGE LEAFLET

1. Name of the veterinary medicinal product

LEISGUARD 5 mg/ml Oral Suspension for Dogs

2. Composition

Each ml contains:

Active substance:	
Domperidone	5 mg
Excipients:	
Methyl parahydroxybenzoate (E218)	1.80 mg
Propyl parahydroxybenzoate	0.20 mg
Quinoline yellow (E-104)	0.20 mg

Yellow suspension.

3. Target species

Dogs

4. Indications for use

To reduce the risk of developing an active infection and clinical disease after contact with *Leishmania infantum*, through the enhancement of the cell-mediated immune response.
The preventive efficacy has been demonstrated in dogs under multiple natural parasite exposure in zones with high infection pressure.

Control of clinical progression of canine leishmaniosis at early stages of the disease (dogs with low to moderate positive antibody levels and mild clinical signs such as peripheral lymphadenopathy or papular dermatitis).

5. Contraindications

Do not use whenever stimulation of gastric motility might be dangerous eg. In the presence of gastrointestinal haemorrhage, mechanical obstruction or perforation.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in animals with prolactin-secreting pituitary tumor.
Domperidone is metabolized by the liver, therefore it should not be administered to patients with liver failure.

6. Special warnings

Special warnings:

In case of severe infections, adequate aetiological treatment should be established in order to lower the parasitic load prior to consider a treatment with this veterinary medicinal product. In all cases, and taking into account the highly variable evolution of the disease, close patient follow up is recommended in order to adapt the treatment to the clinical stage of the animal, as required.

Special precautions for safe use in the target species:

Administration of this veterinary medicinal product produces a transitory increase in plasma prolactin and could induce endocrine disturbances such as galactorrhoea. Therefore it should be used with caution in animals with previous episodes of pseudopregnancy.

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

People with known hypersensitivity to domperidone or to any of the excipients should avoid contact with the veterinary medicinal product.
In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
If you develop symptoms following exposure such as skin rash, you should seek medical advice and show this warning to the physician. Swelling of the face, lips or eyes, or difficulty with breathing are more serious symptoms and require urgent medical attention.
Do not smoke, eat or drink while handling the product.

Pregnancy:

Laboratory studys in laboratory animals have not produced any evidence of teratogenic or foetotoxic effects. Signs of maternal toxicity were not seen in laboratory animals at doses 20 times higher than the recommended dose. However, there are no adequate and well controlled studies in pregnant bitches; therefore use only in accordance with the benefit/risk assessment by the responsible veterinarian.

Lactation:

Administration of domperidone to lactating females of several species has been shown to induce an increase of milk production. Administration of the veterinary medicinal product to lactating bitches is likely to induce the same effect.

Interaction with other medicinal products and other forms of interaction:

Cabergoline is a dopamine agonist that inhibits prolactin release from the pituitary gland. Therefore, its effects are antagonistic to those of domperidone.
Do not administer with stomach antacids such as omeprazole, cimetidine, or antacids
Domperidone should not be used with dopaminergic drugs such as dopamine or dobutamine

Overdose:

In tolerance trials performed in dogs, this veterinary medicinal product has been administered at five times the recommended doses during periods up to one year with no noticeable adverse events.

Special restrictions for use and special conditions for use:

Administration conditions: To be administered by a veterinary surgeon or under their direct responsibility .

Major incompatibilities:

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

7. Adverse events

Dogs:

Rare (1 to 10 animals / 10,000 animals treated):	Mammary gland disorders (mammary hyperplasia and milk production increase)[1] Apathy[2], Appetite loss[2] Abdominal pain, Diarrhoea, Emesis
Very rare (<1 animal / 10,000 animals treated, including isolated reports):	Behavioural disorders

[1]This is considered a consequence of the prolactine peaks induced by domperidone, which disappear after treatment discontinuation.
[2]These signs disappear once the treatment is withdrawn.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you think that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system.

8. Dosage for each species, routes and method of administration

0.5 mg/kg/d, equivalent to 1 ml/10 kg of Leisguard, once daily, during 4 consecutive weeks.

Shake well before use.

The veterinary medicinal product may be administered directly into the mouth or mixed with food. To ensure a correct dosage, body weight should be determined as accurately as possible

PREVENTION:

In healthy animals, a treatment during 4 consecutive weeks induces an activation of the cell-mediated immune response leading to the establishment of an effective barrier against infection in case of eventual exposure to the parasite.

Therefore, in seronegative animals that have never showed any sign of *Leishmania* spp.
infection, but live or travel to an endemic area, strategic domperidone treatments should be programmed, taking into account the temporary prevalence of leishmaniosis vectors *(Phlebotomus* spp.*)* in the geographic area of the patient location or destination.

In high prevalence areas or in climates with a long infective season, one treatment every fourth months is efficacious in preventing the infection and development of the disease. For optimum prevention in the Mediterranean area, it is advised to treat in June, October and February.
In low prevalence areas, one treatment period at the beginning of the infective season and another treatment shortly after its end may suffice.

In all cases, the treatment strategy must be established by the attending veterinarian in accordance with the local incidence of the disease and temporary presence of the infective vectors.

TREATMENT:

In seropositive animals with low to moderate positive antibody levels and mild clinical signs (such as peripheral lymphadenopathy or papular dermatitis), treatment during 4 consecutive weeks is effective for the control of the clinical progression of the disease. In these cases, Leisguard treatment should be

started immediately after diagnosis in order to help animals to self-limit the disease. Improvement of clinical signs is gradually achieved during the following weeks after the end of treatment.

Treatment with Leisguard may be repeated as needed, in accordance with the clinical and serological follow up performed by the attending veterinarian.

9. Advice on correct administration

Shake well before use

10. Withdrawal period

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children
Store in the original package.
Protect from light
The expiry date refers to the last day of that month. Do not use this veterinary medicinal product after the expiry date which is stated on the carton after EXP. The expiry date refers to the last day of that month.
Shelf-life after first opening of the immediate packaging: 8 months.

12. Special precautions for the disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask you veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription

14. Marketing authorisation numbers and pack sizes

DIVASA-FARMAVIC, S.A.:

Package sizes:
Carton box with 1 bottle of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 2 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 3 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 4 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
SINCROFARM, S.L.:

Package sizes:
Carton box with 2 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 3 bottles of 60 ml and 2 syringes of 1.5 and 5 ml
Carton box with 4 bottles of 60 ml and 2 syringes of 1.5 and 5 ml

Not all pack sizes may be marketed

15. Date on which the package leaflet was last revised

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

Ecuphar Veterinaria S.L.U.
C/Cerdanya, 10-12 Planta 6º
08173 Sant Cugat del Vallés
Barcelona, Spain
Tel.: +34 935 95 50 00
E-mail: info@ecuphar.es

Manufacturer responsible for batch release:

DIVASA-FARMAVIC, S.A.
Ctra. Sant Hipòlit, km 71
08503 Gurb-Vic, Barcelona (Spain)

Or

SINCROFARM, S.L.
C/ Mercurio, 10 (Pol. Ind. Almeda).
08940 Cornellà de Llobregat (Spain)