ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kelevo 800 µg tablets for dogs
Kelevo 800 microgram tablets for dogs (AT, DE, PL)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
Levothyroxine sodium 800 µg
(equivalent to levothyroxine 778 µg)

Excipients:

Qualitative composition of excipients and other constituents
Calcium hydrogen phosphate dihydrate
Magnesium stearate
Cellulose, microcrystalline
Croscarmellose sodium
Natural meat flavour (yeast extract)

White to off white, round and convex tablet with brown spots and a cross-shaped break line on one side. The tablets can be divided into 2 or 4 equal parts.

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

Treatment of primary and secondary hypothyroidism.

3.3 Contraindications

Do not use in dogs suffering from uncorrected adrenal insufficiency.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

3.4 Special warnings

The diagnosis of hypothyroidism should be confirmed with appropriate tests.

3.5 Special precautions for use

Special precautions for safe use in the target species:

A sudden increase in demand for oxygen delivery to peripheral tissues, plus the chronotropic effects of levothyroxine sodium, may place undue stress on a poorly functioning heart, causing decompensation and signs of congestive heart failure.

Hypothyroid animals with concurrent hypoadrenocorticism have a decreased ability to metabolise levothyroxine sodium and therefore an increased risk of thyrotoxicosis. These animals should be stabilised with glucocorticoid and mineralocorticoid treatment prior to treatment with levothyroxine sodium to avoid precipitating a hypoadrenocortical crisis. After this, thyroid tests should be repeated, then gradual introduction of levothyroxine is recommended (starting with 25 % of the normal dose and increasing by 25% increments every fortnight until optimal stabilisation is achieved). Gradual introduction of therapy is also recommended for animals with other concurrent illnesses; particularly in animals with cardiac disease, diabetes mellitus and renal or hepatic dysfunction.

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

This veterinary medicinal product contains a high concentration of levothyroxine sodium and may be harmful when ingested, particularly for children. Pregnant women should handle this veterinary medicinal product with caution. Any unused tablet portion(s) should be returned to the open blister, inserted back into the outer packaging and stored out of the sight and reach of children and always be used at the next administration.
In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after handling the tablets.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dogs:

Undetermined frequency (cannot be estimated from the available data):	Pruritus[1]

[1] Initially; exacerbation of skin symptoms with increased pruritus by shedding of the old epithelial cells.

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 its local representative 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 and lactation:

The safety of the veterinary medicinal product has not been established in pregnant or lactating bitches and therefore use of the veterinary medicinal product in these animals should be based on a benefit-risk assessment by the responsible veterinarian. However, levothyroxine is an endogenous substance and thyroid hormones are essential for the developing foetus, especially during the first period of gestation. Hypothyroidism during pregnancy may result in major complications such as foetal death and a poor perinatal outcome. Maintenance dose of levothyroxine sodium may need adjustment during pregnancy. Pregnant bitches should therefore be monitored on a regular basis from conception until several weeks after delivery.

3.8 Interaction with other medicinal products and other forms of interaction

A variety of drugs may impair plasma or tissue binding of the thyroid hormones or alter thyroid hormone metabolism (e.g. barbiturates, antacids, anabolic steroids, diazepam, furosemide, mitotane, phenylbutazone, phenytoin, propranolol, large doses of salicylates and sulphonamides). When treating animals that are receiving concurrent medication the properties of these drugs should be taken into consideration.
Oestrogens may increase thyroid requirements.
Ketamine may cause tachycardia and hypertension when used in patients receiving thyroid hormones.
The effect of catecholamines and sympathomimetics is increased by levothyroxine.
An increase in the dosage of digitalis may be necessary in a patient that had previously compensated congestive heart failure and that is placed on thyroid hormone supplementation. Following treatment of hypothyroidism in patients with concurrent diabetes, careful monitoring of diabetic control is recommended.

Most patients on chronic high-dose, daily glucocorticoid therapy will have very low or undetectable serum T4 concentrations, as well as subnormal T3 values.

3.9 Administration routes and dosage

Oral use.
The recommended starting dose for dogs is 20 µg levothyroxine sodium per kg body weight per day given as a single daily dose or in two equally divided doses.

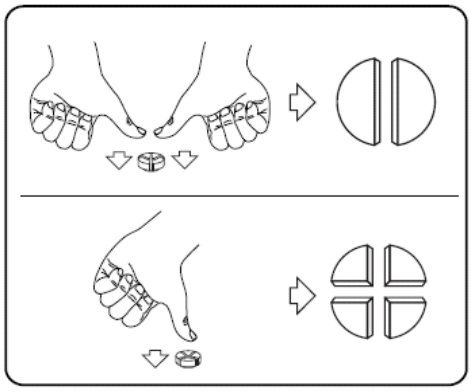
Because of variability in absorption and metabolism, the dosage may require alterations before a complete clinical response is observed. The initial dosage and frequency of administration are merely a starting point. Therapy has to be highly individualised and tailored to the requirements of the individual animal especially for small dogs, in accordance with monitoring by the veterinarian.

In the dog, absorption of levothyroxine sodium may be affected by the presence of food. The timing of treatment and its relation to feeding should therefore be kept consistent from day to day.

Information for the treating veterinarian
For small dogs, it is recommended to use the lower strength 200 µg tablet when commencing therapy and for subsequent dose adjustments given that more accurate dosing and dose titration is possible.

Therapeutic monitoring
The dose should be adjusted based on clinical response and plasma thyroxine levels.
To adequately monitor therapy, trough values (just prior to treatment) and peak values (about four hours after dosing) of plasma T4 can be measured. In adequately dosed animals peak plasma concentration of T4 should be in the high-normal range (approximately 30 to 47 nmol/l) and trough values should be above approximately 19 nmol/l. If T4 levels are outside this range the levothyroxine sodium dose can be adjusted in 50 to 200 µg increments until the patient is clinically euthyroid and serum T4 is within the reference range. Plasma T4 levels can be retested two weeks after change of dosage, but clinical improvement is an equally important factor in determining individual dosage and this will take four to eight weeks. When the optimum replacement dose has been attained, clinical and biochemical monitoring may be performed every 6 – 12 months.

Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



Halves: press down with your thumbs on both sides of the tablet.
Quarters: press down with your thumb in the middle of the tablet.

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

Following administration of overdoses thyrotoxicosis could occur. Thyrotoxicosis as a side effect of mild over-supplementation is uncommon in dogs, owing to the ability of this species to catabolise and excrete thyroid hormones. In case of accidental intake of large amounts of the veterinary medicinal product absorption can be decreased by induction of vomiting and oral administration of both activated charcoal and magnesium sulphate once.

In an acute overdose situation in dogs, the clinical signs are extensions of the hormone's physiological effects. Acute overdose of levothyroxine may produce vomiting, diarrhoea, hyperactivity, hypertension, lethargy, tachycardia, tachypnoea, dyspnoea, and abnormal pupillary light reflexes.

Following chronic over-supplementation in dogs, clinical signs of hyperthyroidism such as polydipsia, polyuria, panting, weight loss without anorexia, and either or both tachycardia and nervousness may theoretically occur. The presence of these signs should result in evaluation of T4 serum concentrations to confirm the diagnosis, and immediate discontinuance of the supplementation. Once the signs have abated (days to weeks), the thyroid dosage has been reviewed, and the animal has fully recovered, a lower dosage may be instituted, with the animal being monitored closely.

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

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code :
QH03AA01

4.2 Pharmacodynamics

Levothyroxine is a synthetic homologue of the naturally occurring thyroid hormone, thyroxine (T4). It is converted to the more biologically active triiodothyronine (T3). T3 binds via specific receptors within the plasma membrane, mitochondria and chromatin resulting in changes in DNA transcription and protein synthesis. Onset of action is therefore slow.

Levothyroxine sodium affects the metabolism of carbohydrates, proteins, fats, vitamins, nucleic acids, and ions. Levothyroxine sodium stimulates the consumption of oxygen and causes an increased metabolic activity by increasing the number of mitochondria. Protein synthesis is stimulated, and the consumption of carbohydrates increases. The fat metabolism is stimulated.

4.3 Pharmacokinetics

After oral intake the gastrointestinal absorption is 10 to 50 % in dogs and C_{max} is reached in 4-12 hours after administration. After administration of 20 micrograms per kg of active ingredient to 57 hypothyroid dogs, the plasma thyroxine (T4) levels increased in the majority of cases to normal values (20-46 nmol). After absorption into the circulation T4 is deiodinated to T3 in the peripheral tissues. In the dog, over 50 % of the T4 produced each day are lost in the faeces. The serum half-life in normal dogs is 10 to 16 hours. In hypothyroid dogs this takes longer.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life of the divided tablets: 4 days.

5.3 Special precautions for storage

Do not store above 30°C.
Store in the original package.
Return unused tablet portion(s) to the open blister and always use at the next administration.

5.4 Nature and composition of immediate packaging

Aluminium – Aluminium blister each with 10 or 25 tablets packed in cardboard box.
Pack sizes:
Cardboard box with 50 tablets.
Cardboard box with 100 tablets.
Cardboard box with 250 tablets.

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

Industrial Veterinaria, S.A.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: {DD/MM/YYYY}

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

{DD/MM/YYYY}

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

{Cardboard box}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kelevo 800 µg tablets

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:

Active substance:

Levothyroxine sodium	800 µg
(equivalent to levothyroxine	778 µg)

3. PACKAGE SIZE

50 tablets
100 tablets
250 tablets

4. TARGET SPECIES

Dogs.

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.
This veterinary medicinal product may be harmful when ingested, particularly for children.
Return unused tablet portion(s) to the open blister and always use at the next administration.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 30°C.
Store in the original package.
Shelf-life of the divided tablets: 4 days.

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

Industrial Veterinaria, S.A.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot {number}

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

{Blister}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Kelevo

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Levothyroxine sodium 800 µg

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Kelevo 800 µg tablets for dogs

2. Composition

Each tablet contains:

Active substance:

Levothyroxine sodium	800 µg
(equivalent to levothyroxine	778 µg)

White to off white, round and convex tablet with brown spots and a cross-shaped break line on one side. The tablets can be divided into 2 or 4 equal parts.

3. Target species

Dogs.

4. Indications for use

Treatment of primary and secondary hypothyroidism.

5. Contraindications

Do not use in dogs suffering from uncorrected adrenal insufficiency.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.

6. Special warnings

Special warnings:

The diagnosis of hypothyroidism should be confirmed with appropriate tests.

Special precautions for safe use in the target species:

A sudden increase in demand for oxygen delivery to peripheral tissues, plus the chronotropic effects of levothyroxine sodium, may place undue stress on a poorly functioning heart, causing decompensation and signs of congestive heart failure.

Hypothyroid animals with concurrent hypoadrenocorticism have a decreased ability to metabolise levothyroxine sodium and therefore an increased risk of thyrotoxicosis. These animals should be stabilised with glucocorticoid and mineralocorticoid treatment prior to treatment with levothyroxine sodium to avoid precipitating a hypoadrenocortical crisis. After this, thyroid tests should be repeated, then gradual introduction of levothyroxine is recommended (starting with 25 % of the normal dose and increasing by 25% increments every fortnight until optimal stabilisation is achieved). Gradual introduction of therapy is also recommended for animals with other concurrent illnesses; particularly in animals with cardiac disease, diabetes mellitus and renal or hepatic dysfunction.

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This veterinary medicinal product contains a high concentration of levothyroxine sodium and may be harmful when ingested, particularly for children. Pregnant women should handle this veterinary medicinal product with caution. Any unused tablet portion(s) should be returned to the open blister, inserted back into the outer packaging and stored out of the sight and reach of children and always be used at the next administration.
In the case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician.
Wash hands after handling the tablets.

Pregnancy and lactation:

The safety of the veterinary medicinal product has not been established in pregnant or lactating bitches and therefore use of the veterinary medicinal product in these animals should be based on a benefit-risk assessment by the responsible veterinarian. However, levothyroxine is an endogenous substance and thyroid hormones are essential for the developing foetus, especially during the first period of gestation. Hypothyroidism during pregnancy may result in major complications such as foetal death and a poor perinatal outcome. Maintenance dose of levothyroxine sodium may need adjustment during pregnancy. Pregnant bitches should therefore be monitored on a regular basis from conception until several weeks after delivery.

Interaction with other medicinal products and other forms of interaction:

A variety of drugs may impair plasma or tissue binding of the thyroid hormones or alter thyroid hormone metabolism (e.g. barbiturates, antacids, anabolic steroids, diazepam, furosemide, mitotane, phenylbutazone, phenytoin, propranolol, large doses of salicylates and sulphonamides). When treating animals that are receiving concurrent medication the properties of these drugs should be taken into consideration.
Oestrogens may increase thyroid requirements.
Ketamine may cause tachycardia and hypertension when used in patients receiving thyroid hormones.
The effect of catecholamines and sympathomimetics is increased by levothyroxine.
An increase in the dosage of digitalis may be necessary in a patient that had previously compensated congestive heart failure and that is placed on thyroid hormone supplementation. Following treatment of hypothyroidism in patients with concurrent diabetes, careful monitoring of diabetic control is recommended.

Most patients on chronic high-dose, daily glucocorticoid therapy will have very low or undetectable serum T4 concentrations, as well as subnormal T3 values.

Overdose:

Following administration of overdoses thyrotoxicosis could occur. Thyrotoxicosis as a side effect of mild over-supplementation is uncommon in dogs, owing to the ability of this species to catabolise and excrete thyroid hormones. In case of accidental intake of large amounts of the veterinary medicinal product absorption can be decreased by induction of vomiting and oral administration of both activated charcoal and magnesium sulphate once.

In an acute overdose situation in dogs, the clinical signs are extensions of the hormone's physiological effects. Acute overdose of levothyroxine may produce vomiting, diarrhoea, hyperactivity, hypertension, lethargy, tachycardia, tachypnoea, dyspnoea, and abnormal pupillary light reflexes. Following chronic over-supplementation in dogs, clinical signs of hyperthyroidism such as polydipsia, polyuria, panting, weight loss without anorexia, and either or both tachycardia and nervousness may theoretically occur. The presence of these signs should result in evaluation of T4 serum concentrations to confirm the diagnosis, and immediate discontinuance of the supplementation. Once the signs have

abated (days to weeks), the thyroid dosage has been reviewed, and the animal has fully recovered, a lower dosage may be instituted, with the animal being monitored closely.

Major incompatibilities:

Not applicable.

7. Adverse events

Dogs:

Undetermined frequency (cannot be estimated from the available data):
Pruritus (itching)[1]

[1] Initially; exacerbation of skin symptoms with increased pruritus (itching) by shedding of the old epithelial (skin) cells.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal 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 or the local representative of the marketing authorisation holder using the contact details at the end of this leaflet, or via your national reporting system: <{national system details}>.

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

Oral use.
The recommended starting dose for dogs is 20 µg levothyroxine sodium per kg body weight per day given as a single daily dose or in two equally divided doses.

Because of variability in absorption and metabolism, the dosage may require alterations before a complete clinical response is observed. The initial dosage and frequency of administration are merely a starting point. Therapy has to be highly individualised and tailored to the requirements of the individual animal especially for small dogs, in accordance with monitoring by the veterinarian.

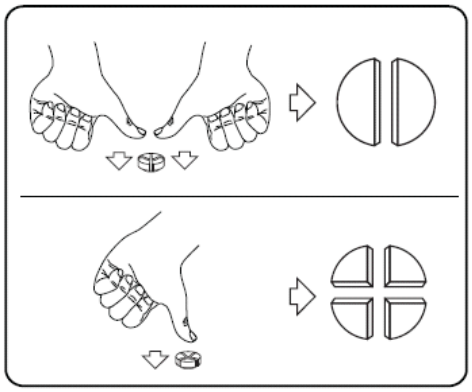
In the dog, absorption of levothyroxine sodium may be affected by the presence of food. The timing of treatment and its relation to feeding should therefore be kept consistent from day to day.

Information for the treating veterinarian
For small dogs, it is recommended to use the lower strength 200 µg tablet when commencing therapy and for subsequent dose adjustments given that more accurate dosing and dose titration is possible.

Therapeutic monitoring
The dose should be adjusted based on clinical response and plasma thyroxine levels.
To adequately monitor therapy, trough values (just prior to treatment) and peak values (about four hours after dosing) of plasma T4 can be measured. In adequately dosed animals peak plasma concentration of T4 should be in the high-normal range (approximately 30 to 47 nmol/l) and trough values should be above approximately 19 nmol/l. If T4 levels are outside this range the levothyroxine sodium dose can be adjusted in 50 to 200 µg increments until the patient is clinically euthyroid and serum T4 is within the reference range. Plasma T4 levels can be retested two weeks after change of dosage, but clinical improvement is an equally important factor in determining individual dosage and this will take four to eight weeks. When the optimum replacement dose has been attained, clinical and biochemical monitoring may be performed every 6 – 12 months.

9. Advice on correct administration

Tablets can be divided into 2 or 4 equal parts to ensure accurate dosing. Place the tablet on a flat surface, with its scored side facing up and the convex (rounded) side facing the surface.



Halves: press down with your thumbs on both sides of the tablet.
Quarters: press down with your thumb in the middle of the tablet.

10. Withdrawal periods

Not applicable.

11. Special storage precautions

Keep out of the sight and reach of children.

Do not store above 30°C.
Store in the original package.
Return unused tablet portion(s) to the open blister and always use at the next administration.
Shelf-life of the divided tablets: 4 days.

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.

12. Special precautions for 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 your 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

XXXXXXX

Pack sizes:
Cardboard box with 50 tablets.
Cardboard box with 100 tablets.
Cardboard box with 250 tablets.

Not all pack sizes may be marketed.

15. Date on which the package leaflet was last revised

{DD/MM/YYYY}

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:
Industrial Veterinaria, S.A.
Esmeralda 19
08950 Esplugues de Llobregat (Barcelona)
Spain
Tel.: +34 93 470 62 70

Manufacturer responsible for batch release:

aniMedica GmbH
Im Südfeld 9
48308 Senden-Bösensell
Germany

aniMedica Herstellungs GmbH
Im Südfeld 9
48308 Senden-Bösensell
Germany

Industrial Veterinaria S.A.
Esmeralda 19
08950 Esplugues de Llobregat (Barcelona)
Spain

LelyPharma B.V.
Zuiveringweg 42
8243 PZ Lelystad
Netherlands

Local representatives and contact details to report suspected adverse reactions: