[Version 9,03/2022] corr. 11/2022

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Forthyron 400 microgram tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:

Active substance:
400µg levothyroxine sodium per tablet (equivalent to 388µg levothyroxine)

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Calcium hydrogen phosphate dihydrate	
Cellulose, microcrystalline	
Sodium starch glycolate (type A)	
Magnesium stearate	

White to off white round tablets, scored on one side
Tablets divisible into 4 parts

3. CLINICAL INFORMATION

3.1 Target species

Dogs.

3.2 Indications for use for each target species

For the treatment of hypothyroidism in dogs.

3.3 Contraindications

Do not use in dogs suffering from uncorrected adrenal insufficiency.

3.4 Special warnings

The diagnosis 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 dogs suffering from hypoadrenocorticism have a decreased ability to metabolise levothyroxine sodium and therefore an increased risk of thyrotoxicosis. Dogs with concurrent hypoadrenocorticism and hypothyroidism 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 therapy, starting with 25% of the normal dose, increasing by 25%

increments every fortnight until optimal stabilisation is achieved is recommended. Gradual introduction of therapy is also recommended for dogs with other concurrent illnesses; particularly diabetes mellitus and renal or hepatic dysfunction.
Restoration of physical activity may unmask or intensify other problems, such as osteoarthrosis.

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

Wash hands after administering the tablets. Pregnant women should handle the product with caution.

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dog

None known.

Adverse reactions of thyroid hormones are generally associated with excessive doses and correspond to the symptoms of hyperthyroidism. See also section 3.10.

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:
The safety of use of the product during pregnancy has not been established through special reproduction studies. 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 base 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 (eg. barbiturates, antacids, anabolic steroids, diazepam, furosemide, mitotane, phenylbutazone, phenytoin, propranolol, large doses of salicylates, and sulphonamides.). When treating dogs that are receiving concurrent medication the properties of these drugs should be taken into consideration.
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.
Estrogens 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.
Following treatment of hypothyroidism in dogs with concurrent diabetes, careful monitoring of diabetic control is recommended.

Most dogs on chronic high- dose, daily glucocorticoid therapy will have very low or undetectable serum T_4 concentrations, as well as subnormal T_3 values.

3.9 Administration routes and dosage

Oral use.

The recommended starting dosage of levothyroxine sodium is 10 µg/kg body weight orally every 12 hour. 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 dog. When initiating dosing of dogs weighing less than 5 kg bodyweight, a quarter of one 200 µg tablet should be administered once daily. Such cases should be monitored carefully. 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. To adequately monitor therapy, trough values (just prior to treatment) and peak values (about three hours after dosing) of plasma T_4 can be measured. In adequately dosed dogs peak plasma concentration of T_4 should be in the high-normal range (approximately 30 to 47 nmol/l) and trough values should be above approximately 19 nmol/l. If T_4 levels are outside this range the levothyroxine dose can be adjusted in 50 to 200 µg increments until the patient is clinically euthyroid and serum T_4 is within the reference range. Plasma T_4 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.

To break a tablet accurately and easily, place the tablet score side up and apply pressure with your thumb.

To break the tablet in two parts; hold one half of the tablet down and press down the other half.

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 oversupplementation is uncommon in dogs, owing to the canine ability to catabolize 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.

Overdoses of three up to six times label recommended starting dose for 4 consecutive weeks in healthy, euthyroid dogs resulted in no significant clinical signs that could be attributed to treatment. Single overdose up to 3-6x the recommended dose does not pose a threat to the dog, and no actions are necessary. However, following chronic over-supplementation, 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 T_4 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

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QH03A A 01.

4.2 Pharmacodynamics

Pharmacologically levothyroxine is classified as a hormonal preparation that replaces deficient endogenous hormones.

Levothyroxine T_4 is converted to triiodothyronine T_3. T_3 acts on cellular processes via specific ligand-receptor interactions with the nucleus, the mitochondria, and the plasma membrane. Interaction of T_3 with binding sites leads to augmented transcription of DNA or modulation of RNA, thus influencing protein synthesis and enzyme action.

Thyroid hormones act on many different cellular processes. In developing animals and human beings, they are crucial determinants of normal development, especially in the central nervous system. Thyroid supplementation increases basal cellular metabolism and oxygen consumption thereby affecting the function of virtually all organ systems.

4.3 Pharmacokinetics

Some dogs appeared to consistently either absorb L-thyroxine better and/or eliminate it more slowly than do other dogs. Furthermore absorption and elimination rate is influenced by daily intake of levothyroxine sodium (high absorption/low elimination in case of low intake and vice versa in case of high intake). The variability in pharmacokinetic parameters between individual dogs is considerable and, although the presence of food may affect absorption, it is considered to have a minor effect on the parameters overall. Absorption is relatively slow and incomplete: In most cases T_{max} occurs between 1 to 5 hours after oral administration, mean C_{max} varies more than 3 fold between dogs on the same doses. In adequately dosed dogs the plasma peak approaches or slightly exceeds the upper limit of normal plasma T_4 levels, and by the end of 12 hours after oral administration, plasma T_4 usually declines to the lower half of the normal range. The rates of disappearance of T_4 from the plasma are slowed in hypothyroidism. A large part of the thyroxine is taken up by the liver. L-thyroxine is bound to plasma-proteins and plasma lipoproteins. Part of a dose of thyroxine is metabolised to the more potent triiodothyronine (T_3) by deiodination. The process of deiodination continues. These further deiodinated metabolic products (other than T_3 and T_4) do not have thyromimetic activity. Other pathways of thyroid hormone metabolism include conjugation to form soluble glucuronides and sulphates for biliary or urinary excretion as well as cleavage of the ether linkage of the iodothyronine molecule. In the dog, over 50% of the T_4 produced each day are lost in the faeces. The extrathyroidal body stores of T_4 are eliminated and replaced in about 1 day.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 18 months
Shelf life after first opening the immediate packaging: 4 days

5.3 Special precautions for storage

Do not store above 25°C.

5.4 Nature and composition of immediate packaging

Blisters, consisting of aluminium foil and a white, opaque PVC/PE/PVDC foil.
10 Tablets per blister, 5, 25, or 50 blisters per carton, 50, 250 or 500 tablets per carton.

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

Eurovet Animal Health B.V.

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

Carton

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Forthyron 200 microgram tablet / Forthyron 400 microgram tablet

2. STATEMENT OF ACTIVE SUBSTANCES

Each tablet contains:
Levothyroxine sodium 200 µg / 400 µg

3. PACKAGE SIZE

50 tablets
250tablets
500 tablets

4. TARGET SPECIES

Dogs

5. INDICATIONS

6. ROUTES OF ADMINISTRATION

Oral use.

7. WITHDRAWAL PERIODS

8. EXPIRY DATE

Exp. {mm/yyyy}

9. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C

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

Eurovet Animal Health B.V.

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

Forthyron

2. QUANTITATIVE PARTICULARS OF THE ACTIVE SUBSTANCES

Levothyroxine sodium 200/400 microgram/tablet

3. BATCH NUMBER

Lot {number}

4. EXPIRY DATE

Exp. {mm/yyyy}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Forthyron 200 microgram tablet
Forthyron 400 microgram tablet

2. Composition

Each tablet contains:
Levothyroxine sodium 200 microgram or 400 microgram

White to off white round tablets, scored on one side
Tablets divisible into 4 parts

3. Target species

Dogs

4. Indications for use

For the treatment of hypothyroidism (under production of thyroid hormone) in dogs

5. Contraindications

Do not use in dogs suffering from uncorrected adrenal insufficiency.

6. Special warnings

Special warnings:
Tell your veterinarian if your dog is suffering from concurrent illnesses, particularly Addison's disease, diabetes mellitus, heart disease or kidney or liver disease.

Information for the treating veterinarian.

The diagnosis hypothyroidism should be confirmed with appropriate tests.

Therapeutic monitoring
To adequately monitor therapy, trough values (just prior to treatment) and peak values (about three hours after dosing) of plasma T_4 can be measured. In adequately dosed dogs peak plasma concentration of T_4 should be in the high-normal range (approximately 30 to 47 nmol/l) and trough values should be above approximately 19 nmol/l. If T_4 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 T_4 is within the reference range. Plasma T_4 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.

Special precautions for safe use in the target species:
The increased metabolic rate resulting from treatment with levothyroxine sodium may place undue stress on a poorly functioning heart, causing signs of heart failure.
Hypothyroid dogs suffering from hypoadrenocorticism (Addison's disease) have a decreased ability to metabolise levothyroxine sodium and therefore an increased risk of overdose. Dogs with concurrent hypoadrenocorticism and hypothyroidism 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 the levothyroxine sodium therapy, starting with 25% of the normal dose, increasing by 25% increments every fortnight until optimal stabilisation is achieved is recommended.
Gradual introduction of therapy is also recommended for dogs with other concurrent illnesses; particularly diabetes mellitus and kidney or liver disease.
Restoration of physical activity may unmask or intensify other problems, such as osteoarthrosis.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
Wash hands after administering the tablets. Pregnant women should handle the product with caution.

Pregnancy:
Tell your veterinarian either if you intend to breed with your dog or your dog is pregnant.
The safety of use of the product during pregnancy has not been established through special reproduction studies. However, levothyroxine is produced naturally in the body and thyroid hormones are essential for the developing foetus, especially during the first period of pregnancy.
Hypothyroidism during pregnancy may result in major complications such as foetal death and a poor outcome at birth. Maintenance dose of levothyroxine sodium may need adjustment during pregnancy.
Pregnant bitches should therefore be monitored on a regular base from conception until several weeks after delivery by the veterinarian.

Interaction with other medicinal products and other forms of interaction:
Tell your veterinarian if your dog is already being treated with any other veterinary medicinal product as this may affect the treatment.
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 dogs that are receiving concurrent medication the properties of these drugs should be taken into consideration.
An increase in the dosage of digitalis may be necessary in a patient that had previously stabilised congestive heart failure and that is placed on thyroid hormone supplementation.
Estrogens 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. Following treatment of hypothyroidism in dogs with concurrent diabetes, careful monitoring of diabetic control is recommended.
Most dogs on long term high- dose, daily glucocorticoid therapy will have very low or undetectable serum T_4 concentrations, as well as subnormal T_3 values.

Overdose:
In case of overdose, contact your veterinarian
Following administration of overdoses signs of toxicity relating to increased levels of thyroid hormone could occur. Toxicity as a side effect of mild oversupplementation is uncommon in dogs, owing to the canine ability to break down and excrete thyroid hormones. Single overdose up to 3-6x the recommended dose does not pose a threat even to the healthy dog with normal thyroid function, and no actions are necessary.
In case of accidental intake of large amounts of tablets absorption can be decreased by induction of vomiting and oral administration of both activated charcoal and magnesium sulphate once.

Following long term over-supplementation, clinical signs of excess thyroid hormone such as increased thirst and urination, panting, weight loss without loss of appetite, and either or both increased heart rate and nervousness may theoretically occur. The presence of these signs should result in evaluation of T_4 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.

7. Adverse events

Dog

None known.

Adverse reactions of thyroid hormones are generally associated with excessive doses and correspond to the symptoms of hyperthyroidism. See also section Overdose.

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 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 dosage of levothyroxine sodium is 10 µg/kg body weight orally every 12 hours. 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 dog, 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.

When initiating dosing of dogs weighing less than 5 kg bodyweight, a quarter of one 200 µg tablet should be administered once daily. Such cases should be monitored carefully by your veterinarian.

9. Advice on correct administration

To break a tablet accurately and easily, place the tablet score side up and apply pressure with your thumb.

To break the tablet in two parts; hold one half of the tablet down and press down the other half.

10. Withdrawal periods

Not applicable

11. Special storage precautions

Keep out of the reach and sight of children.

Do not store above 25 °C
Shelf life after first opening the immediate packaging: 4 days
Do not use this veterinary medicinal product after the expiry date which is stated on the carton and the blister 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

Forthyron 200 microgram: MAH number
Forthyron 400 microgram: MAH number

10 Tablets per blister, 5, 25, or 50 blisters per carton, 50, 250 or 500 tablets per carton.
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:
Eurovet Animal Health BV
Handelsweg 25, 5531 AE Bladel
The Netherlands

Manufacturer responsible for batch release:
Eurovet Animal Health BV
Handelsweg 25, 5531 AE Bladel
The Netherlands

Genera Inc.
Svetonedeljska cesta 2, Kalinovica
10436 Rakov Potok, Croatia

Only the site testing and releasing the batches will be mentioned on the printed leaflet.

<Local representatives <and contact details to report suspected adverse reactions>:>

<For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.>

17. Other information