The European Agency for the Evaluation of Medicinal Products
Veterinary Medicines Evaluation Unit

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COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

LEVOTHYROXINE

SUMMARY REPORT

1. Levothyroxine (3,5,3´,5´-tetraiodo-L-thyronine, thyroxine, T_4) is chemically identical with the natural thyroxine hormone, which is synthesised in the thyroid gland. In veterinary medicine the claimed indications for levothyroxine, in combination with 3,5-diiodo-L-thyrosin, are activation of metabolism and digestion. It is used in treatment of insufficient milk excretion, loss of weight, chronic indigestion and convalescence in cattle and pigs. It can also be used in other species. Levothyroxine is administered orally as a single treatment divided into two daily doses. It is given as a powder mixed with the diet, water or sugar-water. The intended dosage level per day in cattle is 0.10 to 0.29 mg/kg bw and in pigs 0.29 to 0.72 mg/kg bw. The treatment can be repeated once, if required, in cattle and for 5 consecutive days in pigs. In humans, levothyroxine is employed in the treatment of thyroid-deficiency states.

2. The secretory products of the thyroid gland are known as iodothyronines. The major product is 3,3´,5,5´-tetraiodo-L-thyronine (thyroxine, T_4), which functions largely as a circulating prohormone to 3,3´,5-triiodo-L-thyronine (T_3). T_3 is secreted in much less quantity from the thyroid gland. This molecule, which provides almost all thyroid hormone activity in target cells, is actually produced mostly in various tissues from thyroxine. The thyroid hormones increase oxygen consumption and heat production to a large extent by stimulating Na^+K^+-ATPase in all tissues except brain, spleen and testis. The thyroid hormones affect a great multiplicity of metabolic processes; carbohydrate, protein, lipid and vitamin metabolism, influencing the concentration and activity of numerous enzymes and the secretion and degradation rates of virtually all other hormones. Thyroid hormones are also crucial for growth and development of the skeleton and central nervous system in foetus and infants.

   The secretion rate of endogenous thyroxine in humans amounts to 90 µg/day (1.5 µg/kg bw). In cows the normal thyroxine secretion rate show a large seasonal variation, it is usually higher during the winter. Normal thyroxine secretion rate in non-lactating dairy cows ranged from 3.3 to 5.5 µg/kg bw/day in one study. In another study performed during the winter the normal thyroxine secretion rate was 6.6 to 13.2 µg/kg bw/day. The physiological plasma concentration of thyroxine approximates 80 µg/l in humans, 60 µg/l in cows and 30 µg/l in swine.

3. After oral administration daily for 13 weeks to cows of 15000 mg thyroprotein (iodinated casein containing 1% thyroxine, corresponding to 150 mg thyroxine), maximum serum concentration of 134 µg/l is reached after 6 days. Concentration is then maintained on a constant level of approximately 80 µg/l throughout the study. Following cessation of thyroprotein treatment, concentration decreases below the endogenous thyroxine level and approaches normal levels 2 weeks after withdrawal of the treatment.

   Following cessation of daily thyroxine injections (route of administration not stated), with a dose corresponding to 150% of thyroxine secretion rate, to cows for 11 to 12 weeks, the uptake of radioactive ^{131}I in the thyroid is blocked for 10-12 days. The ^{131}I uptake reaches normal levels 3 weeks after cessation of treatment.

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The absorption rate after oral administration of thyroxine in cows is relatively slow. The absorption follows two phases, one rapid and one slow phase, lasting for about 45 hours. This is followed by a declining phase with a plasma half-life of 160 hours. The half-life of thyroxine after intravenous administration is 2.5 days in dairy cows and the turnover rate is 28.4%/day. In cattle thyroxine has a low oral biological effectiveness. The effect after oral treatment of cows is only 10% of that found after subcutaneous injections.

In humans the half-life of thyroxine after oral administration is 6 to 7 days. At hypothyroidism and hyperthyroidism in humans the half-life is 9 to 10 days and 3 to 4 days, respectively.

In human blood thyroxine is bound extensively (more than 99.95%) to plasma proteins. Approximately 60% is bound to T_4-binding inter α-globulin and 30% is bound to T_4-binding prealbumin and about 10% is bound to serum albumin. In cattle, swine, sheep and horses thyroxine is primarily bound to α-globulin. In humans the absorption of thyroxine from the gastrointestinal tract varies between 75 to 85%. The bioavailability of thyroxine decreases by approximately 35% when taken with food.

Thyroxine is metabolised by different mechanisms in humans. Approximately 80% of the metabolism of thyroxine and the various products derived from it proceeds by enzymatic monodeiodination, which yield in the initial step the more active hormone T_3 (35%) and the inactive 3, 3´,5´-triiodo-thyronine (rT_3, 40%). Minor pathways for inactivation of thyroxin and T_3 are conjugation with glucuronic acid and in small amounts with sulphuric acid, decarboxylation and/or deamination.

4. Studies on acute toxicity and repeated dose toxicity are not provided. However, as levothyroxine is an endogenous substance these data were not considered necessary.

5. The lactational response in lactating cows was studied following administration of thyroxine. Initially a single subcutaneous dose of 26 to 51 µg thyroxine/kg bw was administered, followed by daily subcutaneous injections of 10 to 20 µg thyroxine/kg bw for 10 weeks (corresponding to 150% of winter thyroxine secretion rate). The mean increase in milk yield at the peak was 27.6% (range 12.1 to 67.9%). Mean body weight loss at termination of the study was 9.7% (range 3.7 to14.2%). This loss was regained within 2 weeks after withdrawal of treatment. The treatment showed no effect on body temperature. However, no statistical analysis of these effects was performed. In another study lactating cows were injected (route of administration is not stated) with thyroxine daily for a period of 11 to 12 weeks. The dose corresponded to 150% of the thyroxine secretion rate. Following cessation of treatment the milk yield decreased precipitously for 10 to 12 days, thereafter a plateau was established. The maximum milk yield decline after the treatment period, animals were followed for 18 days following treatment, ranged from 39.2 to 68.1%.

   Information from old publications, concerning the lactational response in cows following oral administration of thyroprotein was provided. However, given the facts that thyroprotein only contains low concentrations of thyroxine (1%) and that the purity of the substance was not stated, it is difficult to draw any conclusions of the effects observed in these studies.

6. Data on reproduction toxicity have not been submitted. However, as levothyroxine is an endogenous substance these data were not considered necessary.

7. While no data on mutagenicity and on carcinogenicity were provided the Committee considered that these data were not necessary as levothyroxine belongs to a group of substances which are recognised not to be mutagenic or carcinogenic and which have no chemical analogy with known carcinogens.

8. Thyroid agents have a long history of safe use in human medicine. In humans thyroxine is used in the treatment of different forms of hypothyroidism. The initial adult dose of thyroxine sodium is 50 or 100 µg daily by the oral route. The dose is slowly increased and the maintenance dose is commonly between 100 to 200 µg daily.

Adverse effects of thyroid hormones are generally associated with excessive dosage and correspond to the symptoms of hyperthyroidism (palpitations, tachycardia, cardiac arrhythmias, loss of weight, anginal pain, tremor, headache, diarrhoea, nervousness, insomnia, sweating, intolerance to heat). All reactions usually disappear on reduction of dosage or temporary withdrawal of treatments.

9. No data were presented on the residues of thyroxine in the tissues of the target animals. However, it is noted that levothyroxine is an endogenous substance.

10. No analytical method for determination of thyroxine in tissues was submitted. An analytical method for thyroxine determination in serum was submitted.

Conclusions and recommendation

Having considered the criteria laid down by the Committee for the inclusion of substances in Annex II of Council Regulation (EEC) No 2377/90 and in particular that:

- levothyroxine is only used in a small number of individual animals and for non-regular treatment,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- levothyroxine is an endogenous substance;

the Committee concludes that there is no need to establish an MRL for levothyroxine and recommends its inclusion in Annex II of Council Regulation (EEC) No 2377/90 in accordance with the following table:

Pharmacologically active substance(s)	Animal species	Other provisions
Levothyroxine	All food producing mammalian species	