EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 July 2014
EMA/CVMP/400926/2014
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

Withdrawal assessment report for

Enthryv (EMEA/V/C/002808/0000)

International non-proprietary name (INN): thiamazole

Procedure No.: EMEA/V/C/002808/0000

CVMP Assessment report with all confidential information removed.
Withdrawal at day 200

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Summary

On 1 March 2013, the applicant Nexcyon Pharmaceuticals Ltd submitted an application for a marketing authorisation to the European Medicines Agency (The Agency) for Enthryv transdermal solution for cats, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 (significant therapeutic, scientific or technical innovation).

The eligibility to the centralised procedure was agreed upon by the CVMP on 11 October 2012 (Article 3(2)(b) of Regulation (EC) No 726/2004) as the applicant showed that the product would constitute a significant therapeutic and technical innovation. The rapporteur appointed was D. Murphy and the co-rapporteur was F. Hasslung Wikström. The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

Enthryv is a transdermal solution for topical application containing thiamazole as the active substance. Enthryv is presented in three strengths of single-use tubes (primary packaging) containing 0.25 ml (18.75 mg), 0.5 ml (37.5 mg) or 0.75 ml (56.25 mg thiamazole) in child-resistant blister packs (secondary packaging), with 8 tubes per outer carton box (tertiary packaging). The target species is cats. The applicant initially applied for the following indication: 'treatment of hyperthyroidism and associated clinical signs in cats'.

On 30 June 2014, Nexcyon Pharmaceuticals Ltd withdrew the application at day 200 of the procedure. In its letter notifying the Agency of the withdrawal of application, the applicant stated the reason for the withdrawal: CVMP considered that the data provided do not allow the Committee to conclude on a positive benefit-risk balance.

Scientific advice

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (DDPS) was presented. All pharmacovigilance activities would be contracted to Elanco Animal Health.

It was accepted that the pharmacovigilance system fulfilled the requirements and provided adequate evidence that the applicant had the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form takes place outside the EEA, at Argenta Manufacturing Limited, New Zealand. The site had a manufacturing authorisation issued on 31st August 2012 by the New Zealand Food Safety Authority. As there is a mutual recognition agreement in place for Good Manufacturing Practice (GMP) between the EU and New Zealand, the site was considered appropriately certified as complying with GMP requirements.

Batch release within the EU takes place at McGregor Cory Ltd., UK, which holds a manufacturing authorisation issued by the UK's MHRA.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on a risk assessment which has taken into consideration the GMP certificate available for the active substance site issued by the German Competent Authority following inspection on 26th March 2012.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification were considered in line with legal requirements.

Part 2 - Quality

Composition

The product is a non-aqueous transdermal solution containing 75 mg/ml thiamazole as the active substance, padimate-O as an excipient (penetration enhancer) and ethanol as the solvent.

Container

The primary packaging is single dose laminated aluminium/plastic opaque tubes sealed with 'twist 'n' use' tips. Three different pack sizes are proposed, 0.25 ml, 0.5 ml and 0.75 ml, in order to allow for dose adjustments based on the clinical response (as detailed in section 4.9 of the SPC). As it is a single-dose product the strengths are expressed as the total quantity of active substance per unit dose, that is, 18.75 mg, 37.5 mg and 56.25 mg thiamazole respectively.

The tubes are packaged within child-resistant foil blisters (secondary packaging), and then in outer cardboard cartons (tertiary packaging). The tubes are supplied in cartons of 8.

The active substance, thiamazole, is of toxicological concern. To minimize the risk for accidental intake by children it is necessary that the product is packaged in a child-resistant container/closure. Although the applicant had not demonstrated compliance with the International Standard (EN 14375) Child-resistant non-recloseable packaging for pharmaceutical products – Requirements and testing, a commitment had been provided that evidence of compliance with this standard would be provided prior to commercialisation of the product.

Development pharmaceutics

The formulation has been developed as a transdermal solution to be applied onto the intact skin of cats. It is a non-aqueous formulation consisting of the active substance, thiamazole, a skin penetration enhancer, padimate-O and the volatile solvent ethanol, which rapidly evaporates following application to the skin.

Formulation development focused on the solubility of the active in various volatile solvents, with and without co-solvents, and using two different skin penetration enhancers, octisalate and padimate-O.

A series of formulations containing different concentrations and combinations of volatile solvents were investigated for the solubility and stability of the active substance. Ethanol was found to appropriate for use in the formulation.

Although both penetration enhancers (octisalate and padimate-O) were used in the development formulations, the majority contained octisalate rather than padimate-O. However, as there is a greater potential for salicylate toxicity in cats following accidental ingestion of product containing octisalate, padimate-O was chosen for the final formulation. Although the decision to use padimate-O rather than octisalate appears to have been made late in the product's development, and therefore further optimisation of the formulation may have been possible, the Committee accepted that the formulation has been demonstrated to be a simple and stable one.

Padimate-O is a new excipient which had not previously been used in veterinary medicinal products within the EU. It is permitted for use in cosmetics, including sun screens and is listed in Annex VII entry 21 of the cosmetics Directive 76/768/EEC (as amended) with a maximum concentration of 8%. Anecdotally it is widely used in lip balm creams. It is also monographed in the USP. Given its accepted use in topical sunscreens at a concentration greater than that used in this formulation (50 mg/ml), its inclusion in this topical formulation was considered acceptable. Target animal and user safety issues relating to this excipient are dealt with in Part 3 of the dossier.

Method of manufacture

The process used to manufacture the product is a simple one involving the sequential dissolution of the active substance and the excipient padimate-O in the solvent ethanol, prior to the filling and sealing of the primary containers. A detailed description of the process was provided.

In-process controls consist of visual confirmation of dissolution of the active substance and the excipient, leak testing of the sealed tubes and fill weight checks. Target fill weights were to be confirmed during process validation following establishment of residual volumes in the tubes at commercial scale. An acceptable process validation protocol was provided for full scale commercial batches.

The applicant had not identified which option for tube seal integrity would be most suitable for the hot air sealing commercial equipment and was therefore unable to describe the in-process controls that would be employed for commercial batches. The applicant had however stated that they would implement any necessary testing during process validation and on-going commercial production to ensure tube integrity. The tube sealing process was still being developed at the commercial scale and critical process parameters and in-process leak testing were still being evaluated and remained to be included in the manufacturing instructions in the dossier. The Committee agreed that prior to any commercialisation, the dossier had to be updated to include the method of tube sealing and the associated in-process controls.

Control of starting materials

Active substance

Thiamazole is the subject of a monograph in the European Pharmacopoeia (Ph. Eur.). A valid certificate of suitability (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM) for the named source was provided for the active substance.

Thiamazole is packed in double layered polyethylene bags closed with plastic ties inside a polyethylene drum. The specification and certificates of analysis provided include tests and appropriate methods to ensure compliance with the Ph. Eur. (and also the United States Pharmacopoeia (USP)) requirements and

were acceptable. The stability data provided were sufficient to support the claimed 5 year retest period for the active substance in the proposed packaging with no specific temperature requirements for storage.

Excipients

Ethanol is widely used as an excipient in pharmaceutical products and its specification complies with the current Ph. Eur. monograph.

Although padimate-O is a new excipient in veterinary medicinal products, it is monographed in the USP and is permitted for use in cosmetics, including sun screens. It was therefore not considered necessary to request further details regarding its manufacture and control.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

TSE declarations were provided confirming that the active substance, thiamazole and the excipients ethanol and padimate-O are manufactured without the use of any materials of animal or human origin. A declaration of compliance with the European Commission Note for guidance for minimising the risk of transmitting animal spongiform encephalopathy agents via veterinary medicinal products (EMEA/410/01 rev 3) was also provided.

Control tests during production

Not applicable.

Control tests on the finished product

Descriptions of the specifications and associated methods used for the control of the finished product were provided. The specifications proposed at release and at the end of shelf life control appropriate parameters for the dosage form and were considered to be acceptable.

The analytical method for the determination of the active substance and its degradation products was well described and had been validated in accordance with VICH requirements. Batch data demonstrating compliance with the specification were provided for two pilot scale and two laboratory scale batches of the 18.75 mg and 37.5 mg strengths, and for two laboratory scale batches of the 56.25 mg strength.

Stability

Stability studies were conducted on two pilot scale and one laboratory scale bulk batches filled into six batches of product: three batches of 18.75 mg tubes, and three batches of 37.5 mg tubes. The studies were conducted in accordance with the relevant stability guidelines. Stability data were available for 24 months long term storage at 25 °C/60% RH and 6 months at accelerated conditions of 40 °C/75% RH.

Stability studies were also conducted on two laboratory scale batches of the 56.25 mg strength product: data were available from 12 months storage at long term 25 °C/60% RH and 6 months storage at accelerated conditions of 40 °C/75% RH.

All stability samples were packaged in the proposed market pack but without the secondary packaging (foil blisters) and without the outer cardboard box. Results to date were all within specification and the stability data provided to date support the proposed shelf life of 24 months.

The applicant committed to place samples from the first three full scale commercial batches on stability, using the same or equivalent stability protocols and in accordance with VICH GL3 requirements, and to report any deviation from the agreed specifications to the appropriate authorities.

No specific temperature storage precautions were required. As the product is packaged in an opaque tube within a foil blister and then in an outer cardboard box, it is adequately protected from light.

Overall conclusions on quality

The dossier provided a suitable description of the formulation of the product and demonstrated that the manufacturing process leads to a stable product with consistent quality.

As the manufacturing method is a simple standard process and validation data on pilot-scale batches were provided, it was accepted that full scale validation may be performed post-approval. Although some issues relating to the sealing of the tubes did remain to be fully addressed, the applicant had committed to provide these post-approval and the Committee considered this to be acceptable.

The active substance was described by a Ph. Eur. monograph and as it is in solution in the product, no additional functionality tests were required.

The two excipients are monographed in either the Ph. Eur. or USP and their specifications were appropriate. Padimate-O is a new excipient which is not currently used in veterinary medicinal products within the EU. It is permitted for use in cosmetics, including sun screens and is listed in Annex VII entry 21 of the cosmetics Directive 76/768/EEC (as amended) with a maximum concentration of 8%. It is also monographed in the USP. Given its accepted use in topical sunscreens at a concentration greater than that used in this formulation, its inclusion in this topical formulation was considered acceptable.

Appropriate information was provided for the packaging materials for these single dose spot-on applicators.

There were no concerns in relation to TSE for any of the ingredients of the product.

The tests listed on the finished product specifications were considered appropriate and would control appropriate parameters for this dosage form. The analytical methods were well described, and validated in accordance with VICH requirements.

Stability data for the active substance and dosage form were sufficient to support the claimed retest period and shelf life respectively.

Although the applicant had not demonstrated compliance with the International Standard (EN 14375) Child-resistant non-recloseable packaging for pharmaceutical products – Requirements and testing, the Committee were satisfied that a commitment had been provided that evidence of compliance with this standard would be provided prior to commercialisation of the product.

The quality data and documentation provided were in accordance with the relevant VICH and EU guidelines.

Part 3 – Safety

The registered WHO INN for the active substance is thiamazole. This is also the Ph. Eur. name for this substance. However, methimazole is the USP pharmacopoeia name and this was used in most publications and studies referenced by the applicant in Parts 3 and 4. In line with the EU convention to use the INN, reference in this report is made to the active substance as thiamazole.

Safety documentation

Pharmacodynamics

See Part 4.

Pharmacokinetics

The applicant provided information on pharmacokinetics of thiamazole by reference to the published literature.

Thiamazole is rapidly and almost completely absorbed following oral administration (> 90% bioavailability in humans). Plasma thiamazole concentrations increase linearly with an increase in oral dose. Thiamazole is negligibly bound to plasma proteins in humans.

Thiamazole is widely distributed throughout the body with highest concentrations in the thyroid and adrenal glands. Thiamazole has also been shown to cross the placental barrier. A foetal:maternal ratio of 1:1 was observed. In addition it was shown that thiamazole distributed into milk where it reached the same concentration as in serum.

Only small amounts of thiamazole or metabolites are found in the faeces, though significant amounts are found in the bile, supporting enterohepatic recycling. Metabolites of thiamazole are also excreted in the urine. The major urinary metabolite is a glucuronide conjugate (36-48%), but other minor metabolites have also been identified.

In cats, thiamazole is rapidly and almost completely absorbed (>80%) following oral administration. The mean serum elimination half-life was calculated to be 6.6 +/- 2.0 h. Since antithyroid drugs inhibit thyroid hormone synthesis only when they are concentrated in the thyroid gland, the serum half-life of these drugs may be of lesser importance than the intrathyroidal drug concentration for adequate control of the hyperthyroid condition. The intrathyroidal residence time of thiamazole has not yet been determined in cats; however, it is expected that there will be a sustained effect on T4 beyond its serum half-life.

Multiple-dose administration did not appear to influence the pharmacokinetics of thiamazole. In man it is suggested that thyrotoxic status does not appear to influence pharmacokinetics; however, it has been reported that cats with hyperthyroidism did show a trend towards faster elimination of the drug compared to normal cats.

In support of the pharmacokinetics of thiamazole via the transdermal route in cats, a number of proprietary pharmacokinetic studies were conducted by the applicant. These are commented on in Part 4.

Toxicological studies

Single dose toxicity

Information on single dose toxicity in laboratory animals was taken from a toxicological review available in the published literature. Acute LD_{50} values for thiamazole after different routes of exposure in mouse and rat ranged from 345 to 2250 mg/kg. It was accepted that thiamazole by any route has limited acute toxic potential in rodents. Effects noted in these studies included neurological effects, somnolence, and general reduced activity.

Repeat dose toxicity

Repeat oral dose toxicity has been studied in the rat. Test animals were fed a diet containing about 9 mg thiamazole per kg (total daily intake) for 1, 3, and 6 months, respectively. Control animals were maintained in parallel. During this study, the treated animals did not show any physical signs of toxicity.

However, changes to the thyroid gland were noted at necropsy: weight of the thyroid gland increased with the duration of exposure; the thyroid glands of treated rats after 1 and 3 months showed diffuse homogeneous hypertrophy and hyperplasia of the follicular cells, decreased colloid, and increased vascularity; after 6 months of exposure to thiamazole, diffuse hyperplasia was noted but also heterogeneity in the size and morphology of the follicles, protrusion of follicular tissue through the gland capsule and into vascular spaces, and the development of follicular nodules. Although the nodules that appeared after prolonged administration of thiamazole had many of the characteristics of neoplasia, the diagnosis was oriented towards nodular hyperplasia.

These changes are obviously the consequence of the mechanism of action of thiamazole. This goitrogenic effect of thiamazole (increase in thyroid size and weight) has been fully documented in humans, mice, chickens and rats. As this study did not assess different doses of thiamazole, it was not designed to establish a NOEL.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Mercaptoimidazoles have been shown to cross the placental barrier. In addition, it was shown that thiamazole distributed into milk where it reached the same concentration as in serum.

The available toxicity data suggest that thiamazole has a potentially negative effect on gestation and peri-post natal development in rats. In addition, thiamazole-induced hypothyroidism may affect spermatogenesis and neonatal development. Thiamazole may be associated with developmental delays and behavioural changes in mice. In humans, following a review of anomalies in children exposed to thiamazole *in utero*, the existence of a related embryopathy has been postulated. However, the risk exposure period was limited to the first 7 weeks of gestation.

Based on available information indicating that thiamazole may affect foetal/neonatal development, the applicant proposed that thiamazole should not be given to pregnant/lactating cats. Given the potential for effects on spermatogenesis, the product would also be contraindicated in breeding animals.

However, there are remaining concerns in regard to reproductive toxicity mainly for the user and other persons that may be in contact with treated cats.

Mutagenicity / genotoxicity

Thiamazole induced chromosomal aberrations in mammalian cells *in vitro*. These effects were only observed at high concentrations (equivalent to >1000 times expected maximum blood concentration in human patients under treatment). An *in vivo* study failed to demonstrate any genotoxic effects.

Carcinogenicity

An overall evaluation of carcinogenic potential was made by the International Agency for Research on Cancer (IARC), based on human and experimental animal data. It was concluded that there was inadequate evidence in humans and limited evidence in experimental animals for the carcinogenicity of thiamazole. Thiamazole was accordingly classified as “not classifiable” as to its carcinogenicity to humans (IARC overall evaluation of the carcinogenicity to humans, Group 3).

Notwithstanding the IARC classification (substance not classifiable), the no-effect dietary level of thiamazole from a 2-year rat study is established at 5 ppm or 0.25 mg/kg/day (assuming a standard rat feed intake of 5 g per 100 g of bodyweight).

Studies of other effects

The potential of thiamazole to induce delayed contact hypersensitivity using the murine Local Lymph Node Assay (LLNA) was investigated. Based on the findings of this study, thiamazole should be considered as a weak sensitizer.

A GLP (OECD 404) study in rabbits showed the Enthryv transdermal solution to be non-irritant for the skin.

In a GLP (OECD 405) study Enthryv was severely irritant when administered by the ocular route to rabbits.

Observations in humans

Thiamazole and related compounds (thionamides) have been used for many years to control hyperthyroidism and associated clinical signs in humans, and there is potential for a wide range of adverse effects in humans. It is reported that thionamides can cause adverse effects in 3 to 5% of patients. In most cases, adverse effects are minor and transient (e.g. skin rash with urticaria or pruritus, mild leucopenia); however, there is the potential for rare, serious adverse effects. The most dangerous effect, which occurs in 0.1-0.5% of patients is agranulocytosis. Other serious adverse effects (aplastic anaemia, thrombocytopenia, lupus-like syndrome, vasculitis) are exceedingly rare. Liver damage and cholestasis are rare reactions to thyroid-inhibiting drugs.

Much of the human safety data presented related to adverse effects associated with therapeutic use.

Toxicity of excipients

The excipients contained in Enthryv include padimate-O (50 mg/ml) and ethanol (to 100%).

Ethanol is a common excipient in liquid dermal and oral veterinary medicinal products available in Europe. At the volume of 95% ethanol as proposed for the clinical formulation, there is negligible concern for systemic toxicity for either cats or humans exposed to the excipient through the recommended use of the product.

The final formulation contains 5% padimate-O and is intended to be given as 0.25, 0.5, or 0.75 ml/cat twice weekly (i.e. q72h, q96h) on a long-term basis. Padimate-O is a new excipient which is not currently used in veterinary medicinal products within the EU. It is permitted for use in cosmetics, including sun screens and is listed in Annex VII entry 21 of the cosmetics Directive 76/768/EEC (as amended) with a maximum concentration of 8%. Anecdotally it is widely used in lip balm creams. Some of the summary data presented by the applicant appear to suggest that padimate-O has photomutagenic potential. However, noting that padimate-O is permitted for use in cosmetics and sun screens at concentrations up to 8%, it is reasonable to assume that the quantity of padimate-O proposed for the clinical formulation is

likely to be of negligible concern for systemic toxicity for either cats or humans exposed to the excipient through the recommended use. However, although the concentration of padimate-O is relatively low in the product, it does have the potential for dermal and ocular irritation. Because of this, the applicant proposed that users should be advised to wash their hands thoroughly with soap and warm water after applying the product. Additional safety data on this excipient were not required.

User safety

A user safety assessment, conducted in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1), was presented. The product is a single dose container with a transdermal solution, and supposed to be applied twice weekly by the animal owner.
Likely user exposure may be ocular, oral or dermal.

Inherent toxicity

For ocular exposure, the applicant provided study results demonstrating that Enthryv is severely irritant when administered by the ocular route. Detailed warnings have been listed in the SPC in regard to this, and information has been included on how to avoid accidental spillage and to immediately flush eyes thoroughly with water after accidental contact. The CVMP considered the proposed user safety statements adequate to mitigate this risk.

Following oral exposure in human patients, the most common non-serious adverse events include rash, urticaria, pruritus, fever, gastrointestinal distress, and nausea. Serious adverse effects include agranulocytosis, arthritis, vasculitis, lupus-like syndrome, other hematologic effects (*e.g.* thrombocytopenia and aplastic anaemia), hepatotoxicity (cholestasis), hypoprothrombinemia, hypoglycemia, and pancreatitis. The most common reactions were listed in the SPC with a recommendation to seek medical attention immediately. Agranulocytosis is considered the side effect of primary concern and was used by the applicant to establish a human NOAEL in adults at 12.5 mg/day (2.7 mg/day for a child). However, while it was accepted that the studies referenced by the applicant indicated that the incidence of agranulcytosis might be dose-dependent, other reports showed side effects in humans receiving much lower doses than the proposed NOAEL of 12.5 mg/day, and the proposed NOAEL was not accepted by the CVMP.

Thiamazole is a suspected human teratogen. In a retrospective study of pregnancy outcomes in 6744 hyperthyroid women, the overall rate of major congenital malformations in the thiamazole exposed group (4.1%, 50 of 1231 infants) was significantly ($p < 0.05$) higher than in the control group (2.1%, 40 of 1906 infants). The mean (standard deviation) thiamazole dosage in the study was 5 (8.1) mg/day, but the mean thiamazole dosage in the mothers of the 20 infants with an anomaly associated with thiamazole exposure (i.e. aplasia cutis congenita, omphalocele, and omphalomesenteric duct) was significantly higher ($p < 0.05$) at 12 (8.3) mg/day. Furthermore, all but 2 of 20 women were taking a dosage of ≥5 mg/day (median of 11.25 mg/day) and the lowest dosage administered was 2.5 mg/day. Based on these data, it would appear that the teratogenic effects of thiamazole are dose-related and the applicant proposes that a LOAEL of 2.5 mg/day can be established for pregnant women. However, given the seriousness of the outcome, CVMP does not accept the use of a LOAEL as the basis for the margin of exposure calculation for pregnant women. In addition, there are no assurances that teratogenic effects will not be seen at doses less than 2.5 mg/day.

Exposure assessment

Dermal exposure was considered the most likely exposure, either by direct exposure to the solution or indirectly via stroking a treated animal, and the applicant provided several studies addressing dermal

exposure. As thiamazole is absorbed through the skin and systemically available, adverse events in humans would be the same as seen following oral exposure.

For the purpose of calculating potential owner exposure due to petting a treated animal, the applicant conducted a study to determine the amount of residual thiamazole that could be dislodged when the same cat was repeatedly wiped with a cotton glove, following twice weekly administration of 56.25 mg of transdermal thiamazole solution (containing 75 mg/ml thiamazole and 50 mg/ml padimate O in ethanol) to cats for 3 weeks. Thiamazole was not measureable (<LLOQ) in any of the pre-dosing (Day -1) cotton glove samples. Over time following dosing, the mean residual thiamazole amounts gradually decreased from 2.91 mg/glove on Day 17 at 2 hours post-dosing to 0.683 mg/glove 3 days later on Day 20, demonstrating that residues of the active substance remain at the application site for several days.

Given that the stroking/petting behaviour of individual cat owners will vary widely, it was questionable whether the design of this study should be considered a reasonable worse case. It is possible that some cats in the home will be petted more often/intensively compared to the exposure scenario used in this study. In addition, it is noted that the first sampling time point was at two hours after the last treatment was applied. Any contact with the cat within two hours of product application will increase the potential for user exposure. It is noted that the proposed SPC carries a recommendation not to handle treated cats within two hours after treatment. Notwithstanding the concerns raised, the study confirms that owners/family members may be exposed to a substantial quantity of the applied dose by petting treated animals. Given the relatively small number of observations, the highest individual glove concentrations, rather than the mean, was used in subsequent user exposure calculations.

In addition to the dermal exposure study, an *in vitro* GLP study (based on OECD 428) using human skin isolates was conducted to estimate the daily absorption of thiamazole in humans under various exposure scenarios. Twelve (12) human palm skin matrices per treatment group were evaluated using a finite dose of unlabelled thiamazole and static Franz diffusion cells. The scenarios investigated included direct application of transdermal thiamazole solution (Group 1), the effect of washing following the direct application of transdermal thiamazole solution (Group 2), and direct skin exposure to the estimated minimum (Group 3) and maximum (Group 4) daily dried thiamazole residue present on cat fur. Permeation into the receiver fluid of the diffusion cell was determined by collection of multiple receptor solution samples over 24 hours. Following the 24 h time point, various additional samples (donor chamber, wash, surface, stratum corneum, epidermis, dermis and receiver chamber) were processed for thiamazole extraction/determination. Based on the findings of the study, the applicant concluded that the study demonstrates that thiamazole is absorbed across palm skin following application of the formulation (Groups 1 and 2) and from a residual dried powder form of thiamazole (Groups 3 and 4) representative of that left on the surface of a cats skin. Furthermore, the study also demonstrated that the formulation being washed from the surface of the skin (5 min after initial application) reduced thiamazole absorption across skin.

The overall conclusions of the study and the estimates of thiamazole in different skin matrices and the receiving fluid were accepted by the CVMP. However, the approach used by the applicant when using these data to estimate user systemic exposure was not accepted. It was argued by the applicant that the amount of thiamazole quantified in the receiver fluid and dermis is a conservative estimate of daily systemic exposure for further user safety assessment. However, no justification for excluding thiamazole retained in the epidermis has been provided (that is, it is unclear why residues in the epidermis are considered by the applicant as being unavailable for absorption). It was noted that, in all scenarios investigated by the applicant, a substantial proportion of the administered dose was recovered in the epidermis (20.99 – 60.29% of the applied dose).

In the relevant guidance document (OECD 428), it is stated: "*Skin absorption may sometimes be expressed using receptor fluid data alone. However, when the test substance remains in the skin at the*

end of the study, it may need to be included in the total amount absorbed." and '*The current approach taken by nearly all regulatory agencies is to determine the dermal absorption value by adding the absorbed dose and the chemical remaining in the application site and surrounding skin following washing. This is appropriate for both in vivo and in vitro studies, unless compelling evidence is presented that demonstrates that at least some portion of the residue in the skin is unlikely to be absorbed. However, there is currently some international disagreement about whether part or all of the test substance should be included in the dermal absorption value that is retained in the stratum corneum and can be removed by tape stripping*.' Further, in the related guidance document (OECD (2004): Guidance Document for the Conduct of Skin Absorption Studies), it is stated: "*Microcirculation is obliterated in in vitro skin. Consequently, dermal tissue can retain penetrating compounds, which would have left the skin to join the systemic compartment in vivo. Thus such retention into the dermis in vitro must be taken into account when calculating absorbed.*"

In view of the above, the approach adopted by the applicant (estimating systemic exposure based on the quantity of test item recovered from the receiving fluid and dermis only) was not accepted by CVMP. It should be assumed that all residue present in skin (with the possible exception of stratum corneum) is available for absorption.

Risk assessment:

The assessment of risk to users is based on the margin of exposure (MOE) concept. The MOE is a ratio which indicates the relative relationship (safety) between the level of human exposure and the no observable (adverse) effect level (NOAEL) determined in appropriate human or laboratory animal studies. The acceptability of the MOE, or the "safety" of the exposure, is determined by benchmarking the MOE against the product of individual Uncertainty Factor(s) that account for identified categories of uncertainty that are inherent to extrapolation of human health risk from laboratory animals, intra human variability, use of an appropriate duration study with the most sensitive species, etc. The default MOE value for protecting against systemic toxicity is typically 100. Where the NOAEL is determined based on human data, the MOE value for protecting against systemic toxicity is reduced to 10.

The applicant calculated MOEs for several exposure scenarios. However, as outlined above, neither the proposed NOAELs nor the various exposure estimates used in those calculations were accepted. Consequently, there remains uncertainty around the MOEs calculated by the applicant.

In conclusion, a risk to users or owners of cats under treatment cannot be excluded:

- Regarding the repeat exposure scenario (contact with the product at the time of product administration), a potential user risk cannot be excluded based on the data presented. Therefore, a recommendation to wear protective gloves when applying the product was added. While the advice to wear impermeable gloves will mitigate this risk, the practicality of this advice for what is a twice weekly life-long treatment is open to question.
- Regarding the scenario for repeat dose exposure due to contact with residual thiamazole at the application site following drying of the solution, a risk to children and adults associated with petting treated animals cannot be excluded based on the data presented. Indeed, notwithstanding the concerns with respect to the proposed NOAEL (2.5 mg/person/day) and the exposure estimates, it is noted that the calculated MOE without hand washing after petting for pregnant adults is less than 10. Any further refinement of NOAEL or exposure estimate to address the points raised will result in a lower MOE, with a likely conclusion that the risk for this category of user/animal owner is unacceptable. It is difficult to envisage any additional practical mitigation measure that would further reduce/eliminate the potential risk. The recommendation to wash hands after petting treated cats does not necessarily eliminate the risk to pregnant individuals. In addition, the practicality of

including a recommendation which relates to the handling of treated animals at times not linked to the timing of product administration is open to question.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided in line with line with the VICH guideline GL6 - Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products (VMPs) - Phase I (CVMP/VICH/592/98-FINAL). Given that the product is for the treatment of cats, the environmental risk assessment can stop in Phase I.

Based on the data provided Enthryv would not be expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Thiamazole has a limited acute toxic potential in rodents. Repeated oral administration of thiamazole showed a goitrogenic effect (increase in thyroid size and weight) in humans, mice, chickens and rats; but did not show any clinical signs of toxicity in rats treated with 9 mg thiamazole per kg (total daily intake) for 1, 3, and 6 months, respectively.

Thiamazole may affect foetal/neonatal development, and the product should therefore not be given to pregnant/lactating cats. Given the potential for effects on spermatogenesis, the product should also not be used in breeding animals.

Thiamazole is a weak sensitizer. In rabbits, Enthryv was severely irritant when administered by the ocular route, but non-irritant for the skin.

In humans, oral treatment with thiamazole is associated with non-serious (rash, urticaria, pruritus, fever, gastrointestinal distress, and nausea) and serious adverse effects with agranulocytosis considered the adverse reaction of primary concern. Thiamazole is also a suspected human teratogen, and safety must be considered in the population of pregnant women.

The solution is applied topically, and absorbed quickly; however, residues of the active substance remain at the application site for several days. There remain serious concerns on the user safety of the product regarding all inputs used for the various MOE calculations (NOAELs, exposure estimates and uncertainty factors) and, as a consequence, a risk to users or owners of cats under treatment cannot be excluded. Indeed, notwithstanding the concerns with respect to the proposed NOAEL and the exposure estimates, the calculated MOE without hand-washing after petting for pregnant adults is less than 10. Any further refinement of NOAEL or exposure estimate to address the points raised will result in a lower MOE, with a likely conclusion that the risk for this category of user/animal owner is unacceptable. It is difficult to envisage any additional practical mitigation measure that would further reduce/eliminate the potential risk.

A Phase I environmental risk assessment (ERA) was provided. Based on the data provided the environmental risk assessment can stop in Phase I. Enthryv would not be expected to pose a risk for the environment when used according to the SPC.

Based on the information presented to date, it is not possible to conclude on safety to the user/animal owner.

Residues documentation

Not applicable

Part 4 – Efficacy

Pharmacodynamics

Thiamazole causes a concentration-dependent inhibition of thyroid hormone synthesis by interfering with the enzyme thyroid peroxidase, blocking the incorporation of iodine into the tyrosyl groups of thyroglobulin and the coupling of di- and mono-iodotyrosines to form thyroxine (T4) and triiodothyronine (T3). The inhibitory action of thiamazole is reversible. Thiamazole does not affect inorganic iodine uptake by the thyroid gland, secretion of preformed T3 or T4 from the thyroid gland, or the thyroid gland tissue itself. It also does not affect the conversion of T4 to T3 in peripheral tissues, so the latter may remain normal even when T4 is reduced. Based on the mechanism of action within the thyroid gland, thiamazole indirectly inhibits the serum total T4 (TT4) concentrations.

It is noted that a number of veterinary medicinal products containing thiamazole have already been approved within the EU for the treatment of hyperthyroidism in the proposed target species (cat), albeit in a different pharmaceutical form (tablets). As such, the pharmacodynamic effects of thiamazole in treating hyperthyroidism are well established.

The pharmacodynamic effects of thiamazole associated with topical application to cats have been considered in a number of the proprietary studies. However, none of the pharmacokinetic studies conducted a comprehensive evaluation of the T4 response in the immediate post-treatment period up to 96 or 168 hours (proposed between treatment intervals). While T4 response was determined in the target animal safety studies, sampling time points were relatively far apart (1 week apart in one study and three weeks apart in two studies). With regards to selecting an appropriate between treatment interval, more intensive monitoring of T4 would be informative (in particular, to determine how quickly T4 concentrations begin to rise after treatment). Ideally, such investigations should be conducted in the hyperthyroid cat.

Development of resistance

Not applicable

Pharmacokinetics

See also Part 3.

In support of the pharmacokinetics of the transdermal thiamazole formulation, a number of proprietary laboratory pharmacokinetics (PK) studies in cats were conducted by the applicant. All but one of these were presented as pilot studies using doses of 37.5 mg thiamazole (or higher) per cat. and included group sizes of four animals or less. One of these was a repeat dose study conducted to GLP standards. The available data confirm that thiamazole is systemically available following administration of the transdermal thiamazole solution.

Absorption from the skin is biphasic with fast and slow absorption half-lives of 6.46 – 15.9 hours, and 4.08 – 10.6 days, respectively; i.e. residues of the active substance may remain at the application site for several days (see also user safety and target animal safety).

Plasma thiamazole accumulation due to repeated twice weekly thiamazole administration is limited. Steady-state plasma concentrations following twice-weekly 0.5 ml (37.5 mg) administration to normal, healthy cats resulted in maximum concentrations between 0.44 and 1.85 μg/ml, and 4-day post-dosing trough concentrations of 0.0397 to 0.264 μg/ml. The systemic bioavailability (F) of the product is approximately 50%. Inter-animal differences and/or changes over time in renal and liver function (as assessed by blood urea nitrogen, serum creatinine, and serum chemistry enzymes) do not appear to affect the clearance (Cl) of thiamazole in cats. The bioavailability-normalized clearance (Cl/F) of the product is estimated to be 59.8 – 81.1 l/day (41.5 – 56.3 ml/min). The available data suggest some variability in thiamazole plasma PK profile between and within cats; however the observed variability probably reflects what can be expected from a topically administered product. Indeed, the variability observed following administration of the transdermal formulation appears to be comparable to the variability in exposure reported for oral thiamazole and carbimazole. Further, it is accepted that serum total thyroxine (TT4) concentrations are only indirectly related to plasma thiamazole concentrations. The applicant suggests that the biological variability in the pharmacodynamics, particularly TT4 sensitivity to thiamazole concentrations, is the predominant factor affecting treatment outcome rather than inter-individual variability in the plasma thiamazole concentrations.

Regarding the potential for the variability in thiamazole exposure to impact on clinical efficacy and target animal safety, it is accepted that this may be best evaluated in the context of a field study, where response to treatment (maintaining TT4 within the accepted normal range) can be monitored over time.

Dose determination / justification

In support of the proposed dose, the applicant presented a series of PK/PD model simulations analysing data pooled together from several studies in healthy cats. From these simulations, the applicant concluded that the recommended starting dosage of topical thiamazole solution in diseased cats would be 37.5 mg/cat applied twice weekly. Following 3 weeks of treatment the dose should be adjusted based on the individual serum total T4 concentrations and clinical response, i.e. either increased or reduced. The maximum proposed dose is 56.25 mg thiamazole administered twice weekly. Dose reductions should be made in a stepwise approach, from 37.5 mg twice weekly to 18.75 mg twice weekly, followed by 37.5 mg once weekly and finally 18.75 once weekly.

The findings from the PK/PD modelling exercise are noted. However, it is not considered pivotal to the efficacy dataset. While such modelling may be used to select proposed dose rates, treatment frequencies and suggested titrations for further testing, appropriateness of the proposed dose rates/regimens must be demonstrated in appropriately designed efficacy (dose confirmatory/field) studies.

Dose confirmation

The applicant conducted a pilot study in the US (PCY03-X-10) to determine or confirm the topical thiamazole dose based on relative serum total thyroxine (TT4) concentrations and safety compared to oral thiamazole in healthy laboratory cats. The study included 5 groups with six healthy (non-hyperthyroid) animals in each group. Four of the groups were administered a transdermal thiamazole formulation at one of the following doses/dose frequencies: 37.5 mg thiamazole/cat twice weekly, 37.5 mg thiamazole/cat once weekly, 18.75 mg thiamazole/cat twice weekly or 18.75 mg thiamazole/cat once weekly. The positive control group was administered thiamazole orally at a dose of 2.5 mg/cat twice daily. The duration of the study was 42 days.

The CVMP noted that this was the only study presented that makes a direct comparison (in terms of plasma thiamazole, T4 response and target animal safety) between the topical application and a positive

control, i.e. oral administration of thiamazole. However, with respect to plasma thiamazole and T4 response, the value of the comparison is limited in that it is based on trough values. A more intensive sampling regimen following dosing would be more informative.

Only two dose intervals for the 37.5 mg dose rate were investigated (once or twice weekly). While it can be accepted that administration of 37.5 mg thiamazole topically twice weekly most closely matched plasma thiamazole concentrations and reduction in T4 observed for the orally administered product, the overall mean reduction in T4 levels from baseline was considerably less following topical application of 37.5 mg thiamazole twice weekly (26%) when compared with oral administration of 2.5 mg thiamazole twice daily (39%). It was unclear, therefore, whether a shorter dose interval (for example every other day application) might be more effective or more closely match twice daily oral administration.

Target animal tolerance

Information on target animal safety from the published literature

Thiamazole administered orally to cats at therapeutic levels (various doses) has been associated with the following adverse effects: anorexia, vomiting, lethargy, excoriations, bleeding, hepatopathy, thrombocytopenia, agranulocytosis, leukopenia, eosinophilia, lymphocytosis, positive ANA (serum antinuclear antibodies), and positive direct antiglobulin test.

The gastrointestinal adverse effects generally developed in the first month of treatment and usually resolved even with continued therapy. Mild clinical side effects associated with thiamazole treatment are relatively common (approximately 15% of cats) and include anorexia, vomiting, and lethargy. In most cats these adverse signs are transient and resolve despite continued administration of the drug. Severe gastrointestinal signs nevertheless persist in some cats, requiring drug discontinuation. Thiamazole is known to be a cause of skin reaction leading to pruritus and excoriation, and self-induced excoriations of the face and neck may develop in a few cats in the first 6 weeks of therapy. Cessation of thiamazole administrations is usually required for their complete resolution.

Liver toxicity is an uncommon but serious reaction that can develop during drug treatment. Thiamazole-induced hepatopathy is characterized by marked increases in serum concentrations of ALT, AST, SAP, and total bilirubin. Clinical improvement, with resolution of anorexia, vomiting, and lethargy, usually occurs within a few days of thiamazole cessation, but jaundice and abnormal serum biochemical tests indicative of liver disease may not resolve for several weeks. Re-challenging with thiamazole will again, in a few days, induce clinical signs and serum biochemical abnormalities indicative of liver disease.

A variety of haematological abnormalities may develop in cats during treatment with thiamazole. The most serious haematological reactions that develop in cats treated with thiamazole include severe thrombocytopenia (platelet count <75,000 cells/mm^3) and agranulocytosis (severe leukopenia with a total granulocyte count <250 cells/mm^3). Most cats that develop severe thrombocytopenia also show concomitant overt bleeding (i.e. epistaxis, oral haemorrhage). Development of agranulocytosis during thiamazole treatment predisposes to severe bacterial infections, systemic toxicity, and fever.

A large percentage of cats receiving thiamazole develop serum antinuclear antibodies (ANA). Ferguson states that the risk of developing ANA appears to increase with the duration of thiamazole treatment and the risk of developing serum ANA also appears to be greater for cats receiving higher daily thiamazole doses. Despite the high prevalence of ANA development during long-term treatment with thiamazole, no clinical signs associated with lupus-like syndrome have been observed in any of these cats.

De novo azotaemia is observed in 15 to 20% of hyperthyroid cats after normalisation of T4: cats with hyperthyroidism have abnormally high glomerular filtration rates (GFR) and treating hyperthyroidism by any method may lead to decrease in GFR.

Target animal safety (TAS) studies conducted using the transdermal thiamazole formulation

The applicant also presented three target animal tolerance studies for the thiamazole transdermal formulation. These studies were conducted in healthy adult cats and investigated tolerance to multiples of the recommended treatment dose and increased treatment frequency.

The pivotal TAS study (PCY03-L-09) was conducted to GLP recommendations, and was broadly in line with VICH GL 43 requirements. In the pivotal study, topical treatment with thiamazole 37.5 (1 x recommended therapeutic (starting) dose, RTD, n=8) to 112.5 mg (3xRTD, n=8) was observed to affect various clinical, laboratory, and pathologic parameters. Cats (n=32) were aged between 1.5-1.6 years and in the bodyweight range 2.15-6.25 kg. Males intended for breeding and pregnant or lactating queens were excluded.

The primary effects attributed to topical thiamazole treatment included decreased food consumption, frequent episodes of vomiting, and skin lesions consistent with thiamazole sensitivity (that is, skin lesions are not limited to application site reactions). The frequency of these effects, in general, increased in a dose-dependent manner. In some animals, the effects were considered to be severe enough to warrant the implementation of measures to improve food consumption and/or subcutaneous fluid administration. Similar effects were observed in one of the pilot TAS studies, in which 7 cats (1xRTD:n=2, 2xRTD:n=2 and 3xRTD:n=3) were withdrawn from the study because of vomiting.

Major changes in clinical pathology parameters included reduced thyroxine concentrations, development of antinuclear antibodies, effects on haematopoiesis, and mild to moderate impairment of renal function.

Enlargement of thyroid glands was noted at necropsy. Various changes were also observed in the haemolymphatic system, including lymphoid depletion in the thymus glands of treated cats, and lymphoid hyperplasia in the spleens and lymph nodes of all treatment groups. Three cats showed abnormal bone marrow at time of death.

While the effects observed in the pre-clinical safety studies can be classed as moderate in severity (given that the gastrointestinal effects were considered to be severe enough to warrant the implementation of measures to improve food consumption and/or subcutaneous fluid administration), the relevance of these findings to the target (hyperthyroid) population is unclear. For this type of product, target animal safety is best evaluated in the context of field studies. However, the findings in regard to thiamazole exposure in healthy cats may have some relevance to potential effects that may be observed in untreated in-contact cats exposed to thiamazole via grooming.

Exposure of untreated in-contact animals

Two studies were conducted to determine the systemic exposure of thiamazole in untreated cats following contact with treated animals. The exposure scenario used by the applicant in the first study was not considered to represent a worst-case scenario and was not considered further here.

In the pivotal study, cats in each of 6 pairs were randomized to 1 of 2 groups, treated or untreated. “Treated cats” in each pair were topically administered 56.25 mg of transdermal thiamazole solution to the dorsal cervical region twice weekly (*i.e.,* Days 0, 3, 7, etc.) for 3 weeks. Treated cats were restrained for 2 minutes following dosing and housed separately from their untreated cohorts for 2 hours post-dosing. Blood samples for serum chemistry and haematology were collected from untreated cats prior to beginning dosing (Day -1) and at study completion (Day 21). Additionally, blood samples for

serum total thyroxine (TT4) and plasma thiamazole concentrations were collected from untreated cats prior to beginning dosing (Day -1) and on multiple occasions (Days 17 to 21) after the final dosing episode on Day 17.

Plasma thiamazole concentrations were not measureable (<LLOQ) in any of the untreated cats in the pre-dosing (Day -1) samples. Mean plasma thiamazole concentrations in untreated cats were low at 0.0361 µg/ml immediately prior to the last dose administration, and then increased to 1.10 µg/ml at 12 hours following the return of the treated cat to the pair housing cage. By 94 hours after return of the treated cats to pair housing, plasma thiamazole concentration in the untreated cats averaged 0.0256 µg/ml. The mean C_{max}, t_{max}, and $AUC_{0\text{-}LLOQ}$ over the 94-hour time period following the return of the treated cats to pair housing were 1.40 µg/ml, 15.7 hours, and 37.9 hr*µg/ml, respectively. Inter-individual variability in plasma thiamazole concentrations was substantial, most likely due to variable behavioural interactions between different pairs of cats, particularly untreated cats grooming the application site of treated cats. Serum TT4 concentrations of untreated cats averaged 2.6 µg/dl pre-dosing and ranged from 1.4 to 1.8 µg/dl during Days 17 to 21. Nearly all TT4 concentrations measured on or after Day 17 in untreated cats were lower than baseline levels of the respective cat. However, all TT4 concentrations remained within the normal reference range (0.8 – 4.7 µg/dl) throughout the study. No clinically significant changes were observed in any of the clinical pathology parameters.

Based on the findings of this study, the applicant concluded that untreated cats grooming and cohabitating in close quarters with cats repeatedly administered 56.25 mg of transdermal thiamazole solution twice weekly did not experience clinically significant changes to TT4 concentrations, serum chemistry or haematology parameters, or animal health effects related to residual thiamazole exposure.

While the study appeared to be of satisfactory quality and allowed for certain definitive conclusions to be made, it did not adequately characterise the potential of in-contact cats to be exposed to the active substance and/or to develop thiamazole-related effects:

- Treated cats were housed separately to untreated cats for two hours post-doing (that is, while the application site is wet). It is likely that any contact during this initial period after treatment would increase substantially the potential for exposure (individual untreated cats were noted grooming the application site of treated cats within minutes following reintroduction to the paired housing). It was noted that the applicant proposed for the SPC to include a recommendation that treated cats be kept separate from untreated cats for two hours post-dosing. In certain households it may be difficult to apply such a recommendation. Therefore, the study design was not considered worst-case.
- No justification was provided for the duration of the study (21 days). Given that the treatment of hyperthyroidism is typically months to years, the exposure duration was too short. Indeed, based on the results presented, effects on TT4 (decrease relative to baseline) in untreated cats were observed; however, the applicant considered the effect observed to be of no clinical relevance. This was not accepted: exposure to thiamazole led to a reduction in TT4 in all treated cats. While the TT4 concentrations remained within the reference range, the duration of exposure was relatively short.
- While no significant clinical abnormalities were observed in this study, eight abnormal animal health observations of diarrhoea and/or vomiting were recorded (all of which were mild and resolved). Due to pair-housing, the observed events could not be attributed to treated or untreated cats. Therefore, it could not be excluded that at least some of these events occurred in untreated cats following exposure to the active substance.
- Critically, thiamazole exposure was not determined in treated cats. Therefore, it was not possible to make a direct comparison between untreated in-contact animals and treated cats. However, comparing the findings of this study to thiamazole pharmacokinetic parameters generated in another

study (PCY03-X-17), it was clear that exposure in untreated in-contact cats can be substantial and of a similar magnitude to that achieved in treated cats.

In conclusion, clinically relevant effects associated with thiamazole exposure in untreated in-contact cats cannot be excluded. Indeed, given the potential extent of systemic exposure in untreated in-contact cats due to grooming (similar magnitude to that achieved in treated cats) and the fact that thiamazole-related effects have been reported in normal cats administered the recommended treatment dose, it is considered that thiamazole-related effects are likely to occur in a proportion of untreated in-contact cats.

To mitigate the risk to the untreated cat, the applicant proposes modifying SPC Section 4.5 (Special Precaution for Use in Animals) to state: "*Use in multiple cat households where mutual grooming is common should be subject to careful benefit-risk assessment by the veterinarian due to the potential risk of topical residual thiamazole ingestion by untreated animals. An untreated animal that grooms the application site of a treated animal could experience lethargy, anorexia, vomiting, or loose stool. In the event of adverse reactions in untreated animals, the owner should seek veterinary care and discontinue treatment*."

The proposed risk mitigation measure is noted. However, it is the opinion of CVMP that the potential for unwanted effects in untreated in-contact animals is understated. Further, it is considered that the only way to eliminate the risk of clinically relevant effects associated with thiamazole exposure to untreated cats in multiple cat households is to contraindicate use in multi-cat households and to avoid situations where untreated cats have access to treated cats.

Field trials

The applicant provided the results of two field studies.

Field study in US and UK (2012)

The first field study (PCY03-C-08) was conducted in accordance with GCP at sites in the US and UK. A total of 130 hyperthyroid cats were enrolled on the study. Cats ranged in age from approximately 7 to 21 years and included 53 males (40.8%) and 77 females (59.2%). All animals were neutered and domestic short-hair was the most predominant breed (78.5% at enrolment). The age, breed and sex of animals included in the study are considered to be sufficiently representative of the target population. The maximum dose rate investigated in the study was 37.5 mg thiamazole/cat twice weekly. Cats returned to the clinic at 3, 6, 12, 18, and 24 weeks for subsequent physical examinations and clinical assessment of improvement.

A control group was not included in this study (other than reference to an historical control with a success rate of 0%). The absence of a control group is considered to be a major weakness in the design of this study.

According to the original study protocol, sample size calculations determined that at least 100 cats were required to provide >90% probability of observing a success rate of ≥50% (based upon an estimated success rate of 56% from data in the published literature and modelling/simulations of preclinical data). The findings of this study indicate an overall treatment success rate of 33.3% (95% CI: 30.1-47.3) at 6 weeks with overall success remaining above 33% at all visit time points.

In support of the level of effectiveness reported in this study, the applicant referred to an FDA freedom of information summary (NADA 141-292) concerning an orally administered product authorized for the treatment of hyperthyroidism in cats, containing thiamazole (Felimazole Coated Tablets). A two-sided 95% confidence interval of 50.9-70.3% for success rate of the comparator product (Felimazole) at 6 weeks is reported (using the same overall treatment success criteria as applied in the current study). The

success rate reported for the comparator product (Felimazole) is considerably higher than that reported in the current study (30.1-47.3%). This finding appears to also concur with the results of the dose confirmation study (no. PCY03-X-10) where the overall mean reduction in TT4 levels from baseline was considerably less following topical application of 37.5 mg thiamazole twice weekly (26%) when compared with oral administration of 2.5 mg thiamazole twice daily (39%). Based on these data, it would appear that the transdermal thiamazole formulation (administered at the maximum recommended treatment dose, 37.5 mg/cat twice weekly) would not be as effective as the authorized oral formulation. With respect to safety, clinical findings were broadly in line with those observed in previous studies (anorexia, emesis, diarrhoea, reduction in heart rate and body temperature). Approximately 57% of cats were reported by their owner to have vomited at least once by week 3. A number of cats were observed to have application site changes (hair change/loss, pruritus, lesions) with 14 cats considered to have abnormal application sites by week 6. The number of affected cats reduced over the course of the study (5 cats considered to have abnormal application sites at week 24). In line with observations from previous studies, serum BUN and creatinine levels were elevated. 58% and 15% of cats had elevated serum BUN and creatinine concentrations, respectively, by the end of the study, with renal disease unmasked in some cats.

Field study in US (2013)(NCY03-C-22)

This was an open-label, multi-centre clinical field study conducted at 5 sites in the US conducted in accordance with the principles of GCP. The objective was to evaluate safety and effectiveness of transdermal thiamazole in hyperthyroid cats administered 37.5 mg twice weekly with dose adjustments (up or down) at 3 & 6 weeks. In light of the outcome of study PCY03-C-08, the protocol for this study allowed for an increase in dose, where required, up to a maximum of 56.25 mg twice weekly. The study duration was 9 weeks. The justification for the conduct of this study, as detailed in the study report, was as a consequence of the inadequate achievement of euthyroid thyroxine (T_4) concentrations or clinical improvement by the candidate formulation in Study No. PCY03-C-08.

One hundred and twenty three client-owned cats were screened, of which 47 were subsequently enrolled to the study. The inclusion criteria were baseline serum total thyroxine (TT4) concentrations ≥ 4.7 µg/dl (≥60 nmol/l) and clinical signs consistent with hyperthyroidism as judged by the examining veterinarian. Following each clinic visit (weeks 3, 6 & 9), dose adjustments could be made depending on TT4 response to treatment. Using a starting dose of 37.5 mg/cat twice per week, stepwise adjustments to dose or frequency were either upwards (56.25 mg, twice weekly) or downwards (18.75 mg twice per week or 37.5 mg once per week). The primary outcome parameter was the proportion of successes at week 6 in the per-protocol sample population. Treatment success defined as the composite endpoint of TT4 ≤ 4.0 µg/dl (51 nmol/l) and clinical assessment of improvement ('better') over baseline. Treatment success rates (along with their two-sided 95% CIs) were determined at each scheduled visit. The treatment was considered effective if the lower bound of the 95% CI was greater than the historical control success rate of 0%.

Eleven cats failed to complete the study: 6 cats withdrawn due to treatment failures, specifically arising from local reactions or sensitivity to thiamazole; 4 cats died/euthanized; and 1 cat was withdrawn due to poor protocol compliance. Baseline TT4 concentrations ranged from 5.0 to 13.4 µg/dl (64 to 172 nmol/l), with a median TT4 concentration of 7.7 µg/dl (99 nmol/l). Overall treatment success rate (TT4 ≤ 4.0 µg/dl [≤ 51 nmol/l] and clinical assessment of improvement) at 6 weeks was 65.1% (95% CIs: 50.2% – 77.6%). The ability to increase the dosage up to 56.25 mg/cat twice weekly from the initial starting dosage of 37.5 mg per cat twice weekly increased the number of successes, with 10 out of 15 cats (66.7%) that increased dosages going from treatment failures at Week 3 or 6 to treatment successes by Week 9.

Based on the findings of this study, the applicant concluded that TT4 concentrations and clinical signs of hyperthyroidism were substantially improved following treatment with transdermal thiamazole solution throughout the 9 week study. Overall treatment success rates in the Per-Protocol Dataset were 68.2%, 65.1% and 61.9% at 3, 6, and 9 weeks, respectively - significantly higher at all weeks than the historical control success rate for untreated hyperthyroidism of 0%.

Notwithstanding the conclusions of the applicant, it was considered that the new field study did not provide satisfactory evidence of an acceptable level of efficacy:

- The study was conducted as a single-arm study. The absence of a control group was considered a major weakness. Given the absence of a control group, the possibility for selection bias, ascertainment bias and reporting bias could not be excluded. In the absence of a controlled study, it is not clear that the transdermal thiamazole solution will be as effective as an authorised oral formulation in reducing TT4 and maintaining euthyroidism. Indeed, in responses to CVMP questions, the applicant acknowledges that the non-inferiority of transdermal thiamazole to an authorized oral product cannot be concluded with certainty.
- The sample size (36 cats on study at 6 weeks) is small;
- The test population in the new study was fundamentally different to the test population in the first study in terms of baseline TT4 concentration (thereby increasing chances of success relative to the first study). Consequently, it was not possible to make direct comparisons with the first field study;
- Based on the lower bound of the 95% confidence interval for the estimate of proportion of successes in the ITT population, it was evident that the proportion of treatment successes (based on 'Overall treatment success') at all time points might have been less than 50%. In the new study, the applicant did not set any minimum criteria to establish effectiveness other than the proportion of successes being greater than 0% (success rate of historical control). Given the existence of effective authorized alternative treatments, this was not considered to be a suitably acceptable criterion for concluding on effectiveness;
- It is acknowledged by the applicant that normalisation of TT4 concentrations is less likely when starting TT4 concentrations are high (> 14.6 μg/dl (> 190 nmol/l)).
- It was not clear, based on the data presented, that treated animals remain stable (TT4 maintained within the accepted reference range) on treatment;
- Notwithstanding the provision to increase dose at 3 and 6 weeks, the percentage of cats in the ITT population considered a laboratory success (i.e. based on TT4 concentrations only) decreased from 68.1% at 3 weeks to 55.3% at 9 weeks, indicating that some cats categorized as a success at week 6 were not successfully controlled at week 9. A longer duration study would have provided further useful information on the ability of this treatment to maintain TT4 within the desired range over time.

Regarding target animal tolerance, it is accepted that the cats recovered from adverse events once therapy was stopped. However, the majority of adverse events requiring cessation of therapy in both field studies involved application site reactions. These reactions often took several weeks to recover, but this was not unexpected given that the integument takes time to recover/heal, and it is expected that continuing exposure to thiamazole will likely have minimal influence on the course of the adverse effect. However, for severe and acute adverse effects (for example, haematological disorders, hepatopathy), immediate cessation of treatment would be desirable. For these cases, there is a remaining concern that continuing exposure to thiamazole due to slow release from the depot in the skin may be detrimental.

Further, it was considered that the available safety data at the maximum recommended treatment dose (in terms of both animal numbers and treatment duration) were inadequate to conclude on the safety of the product.

Overall conclusion on efficacy

Thiamazole is an imidazole derivate, causing a concentration-dependent inhibition of thyroid hormone synthesis. The inhibitory action of thiamazole is reversible. The pharmacodynamic effects of thiamazole in treating hyperthyroidism in cats are well established.

The CVMP considered that for this type of product, target animal safety was best evaluated in diseased animals in the context of field studies. The majority of adverse events in both field studies involved application site reactions, which resolved within a period of weeks after therapy was discontinued. However, for severe and acute adverse effects (for example, haematological disorders, hepatopathy), immediate cessation of treatment would be desirable, and concerns remain that continuing exposure to thiamazole due to slow release from the depot in the skin may be detrimental for these cats. In addition, as only very limited field safety data were available at the recommended maximum treatment dose of 56.25 mg/cat (twice weekly), the CVMP considered the data inadequate to conclude on the safety of the highest proposed is dose.
In conclusion, based on available data, potential risks to the target animal associated with use of the product according to the proposed posology have not been adequately characterised.

In healthy, untreated cats, which were in contact with cats treated for 3 weeks, twice per week, decreased TT4 plasma levels were noted. Although these did not result in clinical signs, data were considered insufficient to allow clear conclusions on the tolerance of animals in contact. Based on the data presented, clinically relevant effects associated with thiamazole exposure in untreated in-contact cats cannot be excluded. Indeed, given the extent of systemic exposure in untreated in-contact cats, and the fact that thiamazole-related effects have been reported in normal cats administered the recommended treatment dose, it was considered that thiamazole-related effects (reduction in TT4, emesis, anorexia, etc) are likely to occur in a proportion of untreated in-contact cats. To mitigate the risk to the untreated cat, the applicant proposes modifying SPC Section 4.5 (Special Precaution for Use in Animals) to state: “Use in multiple cat households where mutual grooming is common should be subject to careful benefit-risk assessment by the veterinarian due to the potential risk of topical residual thiamazole ingestion by untreated animals. An untreated animal that grooms the application site of a treated animal could experience lethargy, anorexia, vomiting, or loose stool. In the event of adverse reactions in untreated animals, the owner should seek veterinary care and discontinue treatment.” The proposed risk mitigation measure is noted. However, it is the opinion of CVMP that the potential for unwanted effects in untreated in-contact animals is understated. Further, it is considered that the only way to eliminate the risk of clinically relevant effects associated with thiamazole exposure to untreated cats in multiple cat households is to contraindicate use in multi-cat households and to avoid situations where untreated cats have access to treated cats.
In conclusion, based on available data, potential risks to untreated in-contact cats cannot be excluded.

In support of the proposed dose, the applicant presented a series of PK/PD model simulations analysing data pooled together from several studies in healthy cats, as well as a pilot study in the US to determine or confirm the topical thiamazole dose based on relative serum total thyroxine (TT4) concentrations. However, all the studies were done in healthy cats, and it was considered that appropriateness of the proposed dose rates/regimens should be demonstrated in appropriately designed efficacy (dose confirmatory/field) studies in diseased animals.

In order to demonstrate the clinical efficacy, two GCP field studies were conducted, one in the US and UK (2012) and a second one in the US (2013). Both studies were conducted using the final transdermal formulation in hyperthyroid cats administered 37.5 mg twice weekly with dose adjustments at 3 and 6 weeks. In the first study, dose adjustments were undertaken to stepwise lower the dose/dosing interval; while in the second study also a higher dose of 56.25 mg thiamazole/cat was tested. Both studies were conducted as single-arm studies. The applicant acknowledges that without a positive controlled clinical trial, the non-inferiority of transdermal thiamazole to an authorized oral product cannot be concluded with certainty. To mitigate the possibility that transdermal thiamazole could be less effective compared to authorised oral anti-thyroid drugs, the applicant acknowledged that they may need to accept modifying the indication to the following: *Treatment of hyperthyroidism in cats where compliance to an oral anti-thyroid therapy cannot be achieved.* CVMP accepted that poor compliance with oral anti-thyroid dosage regimens is an issue for some cat owners/cats and that this may have a clinically relevant impact on efficacy and/or lead to withdrawal of treatment. Therefore, the applicant proposed that this product could be indicated as a last line treatment for those cats. CVMP accepted that transdermal thiamazole may offer an appealing alternative to oral treatments where compliance is an issue, in particular for cats that are difficult to administer a pill. However, notwithstanding the appeal of transdermal thiamazole for the treatment of cats where compliance to an oral anti-thyroid therapy cannot be achieved, CVMP considered that the revised indication should not be accepted on the basis that the applicant has provided inadequate proof of efficacy:

- The sample population in the pivotal efficacy study (NCY03-C-22) that allowed for the highest dose is very small (36 cats on study at 6 weeks).
- In the absence of a controlled study, it is not clear that the transdermal thiamazole solution will be as effective as an authorised oral formulation in reducing TT4 and maintaining euthyroidism. Indeed, the applicant acknowledged that the non-inferiority of transdermal thiamazole to an authorized oral product cannot be concluded with certainty.
- Further, it was acknowledged by the applicant that normalisation of TT4 concentrations is less likely when starting TT4 concentrations are high (> 14.6 μg/dl (> 190 nmol/l)).
- There are inadequate assurances that stable euthyroidism can be achieved in treated cats. Further, in the pivotal study, test animals were only followed up to week 9.

In conclusion, based on the data available, the CVMP considered that the applicant did not provide satisfactory evidence of an acceptable level of efficacy.

Part 5 – Benefit-risk assessment

Introduction

Enthryv is a transdermal solution for topical application to cats containing thiamazole as the active substance. The route of administration is transdermal use.

Enthryv is presented in three strengths of single-use tubes (primary packaging) containing 0.25 ml (18.75 mg), 0.5 ml (37.5 mg) or 0.75 ml (56.25 mg thiamazole) in child-resistant blister packs (secondary packaging), with 8 tubes per outer carton box (tertiary packaging).

The applicant applied for the following indication '*treatment of hyperthyroidism and associated clinical signs in cats*'. During the assessment procedure, the applicant proposed that the indication be amended to the following: '*Treatment of hyperthyroidism in cats where compliance to an oral anti-thyroid therapy cannot be achieved.'*

The application has been submitted in accordance with Article 12(3) of Directive 2001/82 (full dossier).

Benefit assessment

Direct therapeutic benefit

The main benefit of Enthryv would be its efficacy in the treatment of feline hyperthyroidism. The pharmacodynamic effects of the active substance thiamazole in treating hyperthyroidism in cats via the oral route are well established.

In support for this novel route of administration via the transdermal route, two new clinical studies were provided; however, none of the studies provided sufficient evidence of efficacy, when Enthryv was administered as recommended, for the treatment of cats with hyperthyroidism (that is, achieving and maintaining euthyroidism).

In conclusion, based on the data available, the CVMP considered that the applicant did not provide satisfactory evidence of an acceptable level of efficacy.

Additional benefits

Enthryv is easy to apply by the owner, which would be a benefit in treating cats where compliance to an oral anti-thyroid therapy cannot be achieved. In addition, it was proposed that the product is administered twice-weekly as compared to daily treatments with the currently available oral formulations. These features would be expected to facilitate owner compliance.

Notwithstanding the appeal of transdermal thiamazole for the treatment of cats where compliance to an oral anti-thyroid therapy cannot be achieved, CVMP is of the opinion that the proposed (revised) indication should not be accepted on the basis that the applicant has provided inadequate proof of efficacy.

Risk assessment

The formulation and manufacture of Enthryv is well described, and the product specifications ensure that a product of an appropriate and consistent quality could be produced. Compliance with the International Standard (EN 14375) “Child-resistant non-recloseable packaging for pharmaceutical products – Requirements and testing” remains to be demonstrated, however that did not preclude a conclusion on the quality part of the application.

The following main potential risks have been identified.

For the target animals:

The product may pose a risk to pregnant, lactating or breeding animals. Consequently, the use of the product would be contraindicated in such animals.

The most common reactions in the target animals are application site reactions and gastrointestinal signs (very common), and changes in blood parameters (common). Most of the effects were reversible and mild. However, thiamazole administration may be associated with serious adverse effects (haematological abnormalities, liver toxicity). In addition, oral thiamazole is known to be a cause of skin reaction leading to pruritus and self-induced excoriation (in particular of the face and neck). *De novo* azotaemia is observed in 15 to 20% of hyperthyroid cats after normalisation of TT4.

For severe and acute adverse effects (for example, haematological disorders, hepatopathy), immediate cessation of treatment would be desirable, and concerns remain that continuing exposure to thiamazole

due to slow release from the depot in the skin may be detrimental for these cases. In addition, as only limited field safety data were available at the recommended maximum treatment dose of 56.25 mg/cat (twice weekly), the CVMP considered the data inadequate to conclude on the safety of the highest proposed dose.

In conclusion, based on available data, potential risks to the target animal associated with use of the product according to the proposed posology have not been adequately characterised.

For in-contact animals:

In healthy, untreated cats, which were in contact with cats treated for 3 weeks, twice per week, decreased TT4 plasma levels were noted. Although these did not result in clinical signs, data were considered insufficient to allow clear conclusions on the tolerance of animals in contact. Based on the data presented, clinically relevant effects associated with thiamazole exposure in untreated in-contact cats cannot be excluded, and it was considered that thiamazole-related effects (reduction in TT4, emesis, anorexia, etc) are likely to occur in a proportion of untreated in-contact cats. It is considered that the only way to eliminate the risk of clinically relevant effects associated with thiamazole exposure to untreated cats in multiple cat households is to contraindicate use in multi-cat households and to avoid situations where untreated cats have access to treated cats.

In conclusion, based on available data, potential risks to untreated in-contact cats cannot be excluded.

For the user:

In human patients, treatment with thiamazole is associated with non-serious (rash, urticaria, pruritus, fever, gastrointestinal distress, and nausea) and serious adverse effects with agranulocytosis considered the adverse events of primary concern. Thiamazole is also a suspected human teratogen and safety must be considered in the population of pregnant women.

There remain serious concerns on the user safety regarding all inputs used for the various margin of exposure (MOE) calculations (NOAELs, exposure estimates and uncertainty factors) and, as a consequence, a risk to users or owners of cats under treatment cannot be excluded (due to contact with the product at the time of product administration and/or exposure to residual thiamazole at the application site following drying of the solution when petting treated animals). Indeed, notwithstanding the concerns with respect to the proposed NOAEL and the exposure estimates, the calculated MOE without hand-washing after petting for pregnant adults is less than 10. Any further refinement of NOAEL or exposure estimate to address the points raised will result in a lower MOE, with a likely conclusion that the risk for this category of user/animal owner is unacceptable.

In conclusion, a risk to users or owners of cats under treatment cannot be excluded.

For the environment:

The product does not pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

Appropriate information has been identified to inform on the potential risks of this product relevant to the environment however due to the inconclusive efficacy data and the outstanding concerns relating to animal and user safety, it was not possible to identify reasonable risk management or mitigation measures that would sufficiently reduce or eliminate the potential related risks.

Evaluation of the benefit-risk balance

The therapeutic benefit remains inconclusive as the efficacy has not been substantiated.

The formulation and manufacture of Enthryv is well described and specifications set will ensure that product of consistent quality will be produced.

The product presents an acceptable risk for the environment when used as proposed and appropriate warnings have been identified for this risk.

There remain, however, serious concerns in regard to the safety of the product for the user, the target animal and animals-in-contact.

In view of the above, the CVMP considered that the potential risks identified out-weight the potential benefits of the product (as demonstrated in available clinical studies). Consequently, the overall benefit risk balance is considered negative.

Conclusion on the benefit-risk balance

Based on the data presented to date, the overall benefit-risk is deemed negative.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality of Enthryv was considered to be in accordance with the requirements of Directive 2001/82/EC, however that safety and efficacy of Enthryv were not considered to be in accordance with the requirements of Directive 2001/82/EC.

The CVMP considers that the benefit-risk balance is negative and, therefore, recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product.