SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

The active substance in Reconcile chewable tablets is fluoxetine hydrochloride, a selective serotonin reuptake inhibitor (SSRI) (ATC vet code: QN06AB03). As a result of inhibiting serotonin reuptake, fluoxetine enhances serotonergic neurotransmission and produces functional effects resulting from increased activation of serotonin receptors.

The approved indication is: "As an aid in the treatment of separation-related disorders in dogs manifested by destruction and inappropriate behaviours (vocalisation and inappropriate defecation and/or urination) and only in combination with behavioural modification techniques."

The benefits of Reconcile are its efficacy in the treatment of separation-related disorders in dogs without causing pronounced sedation. When used in combination with behavioural modification techniques a clinical improvement is usually seen within 1 to 2 weeks and has been demonstrated for up to 8 weeks treatment with fluoxetine. The treatment is given orally once a day and the tablets, which are chewable, may be given with or without food. The most common side effects are decreased appetite (including anorexia) and lethargy.

2. QUALITY ASSESSMENT

Composition

Reconcile chewable tablets for dogs are available in four different strengths, containing 8 mg, 16 mg, 32 mg and 64 mg fluoxetine (included in the form of fluoxetine hydrochloride).

The tablets include commonly used tablet excipients. These are listed in section 6.2 of the Summary of Product Characteristics (SPC), and their functions in the product are: microcrystalline cellulose (diluent); compressible sugar (binder); crospovidone (disintegrant); an artificial beef flavour (a flavouring commonly used in tablets for dogs); colloidal silicon dioxide (glidant); dibasic calcium phosphate dihydrate (diluent); and magnesium stearate (lubricant). All four strengths of tablet are manufactured from a common blend.

Container

The tablets are supplied in white high density polyethylene (HDPE) bottles, each with a child resistant closure. Each bottle contains 30 tablets and is fitted with a cotton coiler and a desiccant canister.

Development Pharmaceutics

The aim was to develop an immediate release palatable tablet formulation for use in dogs. In order to cover the whole target dog weight range there are four strengths of tablets (8, 16, 32 and 64 mg).

The active ingredient, fluoxetine hydrochloride, is sensitive to the presence of water, therefore, a directly compressible tablet blend has been developed to avoid the need for granulation. The excipients used are all very commonly used in tablets. From experience with human formulations, crospovidone was known to be compatible with the active substance. Studies in dogs with different concentrations of artificial beef flavour dictated the content in the final tablets formulation that would be optimal for palatability. The compatibility of the chosen excipients with the active substance has been demonstrated and supported by stability studies. Although artificial powdered beef flavour is hygroscopic, stability data showed that the water content of the tablets is well controlled.

Final process development and full scale batch manufacturing took place at the site for commercial manufacture.

Method of manufacture

A conventional dry mixing process is used to blend the active substance and excipients. Direct compression of the final lubricated blend into tablets then follows. Full details were provided of the manufacturing process and standard batch sizes.

Validation studies on commercial scale batches of the tablets demonstrated the manufacturing process was robust and led to consistent products which met their approved specifications.

CONTROL OF STARTING MATERIALS

Active substance

The active substance fluoxetine hydrochloride (a racemic mixture, 50:50 R:S) is well known from human medicine and is the subject of a Ph.Eur. Certificate of Suitability which includes additional tests and limits (in line with the requirements of the residual solvents guideline VICH GL18 and its EU Annexes) for the solvent dimethylacetamide (DMAC), and also for two potential impurities (degradation products). All potential impurities are fully discussed and are quantified using suitably validated methods.

No method validation data were required for the Ph.Eur. methods used in the specification. Validation of the method used for the determination of DMAC has been assessed during the EDQM certification for this manufacturer of fluoxetine hydrochloride. The reference standards have been characterised and detailed.

The impurities which could be present are listed in the Ph.Eur. monograph for fluoxetine hydrochloride. In addition to the mentioned impurities there are two potential degradation products:

- P-Trifluoromethylphenol occurs under acidic (and oxidative) conditions, has not been found in recent batches but is named in the Ph.Eur. monograph. This potential degradation product is observed in some of the tablet batches and is used for system suitability criteria purposes for the related substances test method.
- N-Formyl fluoxetine is the prominent degradation product observed in the finished product tablets. It is possible it might be formed via a Maillard reaction mechanism from reducing (sugar) components in the compressible sugar and/or beef flavour. (The generation of this impurity has already been shown if reducing sugars such as lactose are present.)

Acetone and DMAC are controlled on a routine basis. The limit applied for acetone is that in the fluoxetine hydrochloride Ph.Eur. monograph. The limit for DMAC is in line with the requirements of the residual solvents guideline (VICH GL18 and its EU Annexes). Batch data confirm compliance with the proposed limits.

Results of three commercial size batches of fluoxetine hydrochloride have been provided, together with certificates of analysis. All the results met the product specification and demonstrate consistency of manufacture.

Several batches of fluoxetine hydrochloride were stored in the commercial packaging at 30°C/60%RH and 30°C/65% RH for 24 months. Testing (assay, related substances (individual and sum), appearance, and water content) was performed according to the Ph.Eur. monograph. The results showed that all batches meet specifications and the fluoxetine hydrochloride content is practically unchanged. No significant changes were found in the levels of the main impurities. In addition, results of 6 months studies performed at accelerated conditions, 40°C/75% RH were provided. No data on testing under long term VICH conditions (25°C/60% RH) were presented but this is acceptable in view of the results obtained at 30°C/60% RH. A retest period of 24 months in the commercial packaging was therefore justified without any further storage recommendation.

A report on stress testing of the active substance was also provided. In the solid state, fluoxetine hydrochloride was shown to be stable under the conditions tested (heat and humidity for up to 28 days, e.g. 70°C/~75% RH; simulated sunlight for up to 20 hours).

Excipients

All the excipients, except the compressible sugar and the artificial beef flavouring, comply with the relevant specification of the appropriate Ph. Eur. monograph. The compressible sugar complies with the relevant US NF specification.

The artificial beef flavour is not described in a pharmacopoeia but is widely used in other veterinary medicinal products authorised in Europe and is satisfactorily controlled by the proposed specification. It is composed of hydrolysed vegetable protein from soybeans, hydrogenated vegetable oil from soybeans and desiccated pork liver powder. The soybean derived components are sourced from non-GMO soybeans only. Full details of the sourcing of the pig livers and their subsequent processing were provided and considered satisfactory. The pig liver powder is sterilised by gamma-irradiation (with well defined, validated dose limits) to eliminate the risk of transferring any viruses or microorganisms from pork liver to the target animal. Routine tests and methods of manufacture have been described both for the artificial beef flavour and also for its components, and these were all acceptable.

Typical certificates of analysis have been provided for all the excipients in Reconcile chewable tablets and these demonstrate compliance with the relevant specifications.

Packaging

From early accelerated stability studies it became apparent that water ingress had to be limited because of the moisture sensitivity of the active substance, therefore, an HDPE bottle with a desiccant canister was chosen for the marketed pack.

The primary container is a white HDPE bottle fitted with a child resistant closure (screw cap with induction heat seal liner) and each bottle contains 30 tablets. All materials coming in contact with the product (LDPE foil, HDPE bottles, heat seal liner, cotton, silica gel canister) have been stated to comply with the relevant EU standards. Batch analytical data of those materials have been provided showing compliance with the relevant Ph.Eur. monographs.

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

Magnesium stearate is of vegetable origin. The active substance fluoxetine hydrochloride is chemically synthesised. The only excipient of animal origin is the artificial beef flavour which contains pork liver (no bovine products). None of the materials used in the manufacture of Reconcile tablets, therefore, carries any TSE risk. Declarations have also been provided that the starting materials used in the production of the final product comply with the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" and Commission Directive 1999/104/EEC.

CONTROL TESTS ON THE FINISHED PRODUCT

The limits are justified by reference to batch analyses and stability data and are all justified. Microbial limits are in accordance with the Ph.Eur. 5.1.4. Tablet hardness, friability, weight and thickness of tablets are monitored as in-process-controls during manufacture. The flavour is hygroscopic so the tablet water content is limited as the active substance is moisture sensitive.

Specifications for testing the finished product (all four strengths of tablets) have been detailed and all the methods described. These include appearance, identity and assay of the active substance content, related substances (impurities and degradation products), dissolution testing, uniformity of dosage

units, moisture content and microbial purity. The limit of degradation products is in accordance with VICH GL11 and justified. It is well documented that N-formyl fluoxetine is the primary degradant and so increases with time over the shelf-life of the product.

The following parameters in the shelf-life specification have different limits from those in the release specification: assay limit; the limit for the degradation product N-formyl fluoxetine (see above); the limit for the sum of impurities; and the water content. All differences have been justified by stability data. The analytical methods applied are those described for finished product testing at release.

Appropriate validation results regarding linearity, specificity, accuracy, precision (repeatability, intermediate precision) are provided.

Analytical results of many pilot scale and commercial scale batches of Reconcile tablets (all strengths) were provided and all results are in accordance with the appropriate specifications and show high batch to batch uniformity of the finished product.

Stability

Comprehensive stability studies have been performed on several batches (up to full commercial scale) of all tablet strengths stored in the commercial packaging (HDPE bottles). Testing has been performed for as long as 27 months at 25°C/60% RH (long term testing), for 12 months at 30°C/60% RH (intermediate testing) and for 6 months at 40°C/75% RH (accelerated testing). The highest water contents were found for the lowest strength tablets (8 mg) as this has the highest tablet surface area to volume ratio and, therefore, would predictably be the most susceptible to moisture uptake.

At accelerated conditions (40°C/75% RH) out of specification results have been reported in two batches in which the N-formyl fluoxetine and total impurity specifications have been exceeded after 6 months. However, after 9 months at intermediate conditions (30°C/60% RH) the findings are still well below the specified (shelf life) limits. Therefore, the following storage conditions are justified: “Do not store above 30°C.”

Fluoxetine hydrochloride itself has been demonstrated not to be sensitive to light exposure and as the tablets are packaged in white opaque HDPE bottles the absence of photostability testing of the finished product has been justified.

The stability data provided justify the proposed shelf-life of 24 months with the following storage restriction: “Do not store above 30°C. Store product in original container. Close tightly after use. Do not remove the desiccant.”

An in-use stability study has been performed using both freshly manufactured batches of Reconcile tablets and batches at the end of their shelf-life. The results justify the in-use shelf life of 30 days.

OVERALL CONCLUSION ON QUALITY

The quality of Reconcile chewable tablets is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for a marketing authorisation. There are no major deviations from the current EU and VICH requirements.

The active substance is a racemic mixture but is well characterised and documented. The other excipients are all commonly used in veterinary tablet formulations and all comply with current Ph.Eur. requirements except the compressible sugar (complies with US NF) and the artificial beef flavouring, for which a satisfactory in-house specification was provided. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. The specifications used for both release and at the end of shelf-life are appropriate to control the quality of the finished product. Stability tests indicate that the product under VICH guidelines conditions is chemically stable for the proposed shelf-life. At the time of the

Opinion one minor issue remained unresolved and it was agreed to be addressed as a post-approval commitment as it does not affect the benefit/risk balance of the product.

3. SAFETY ASSESSMENT

Pharmacokinetics

The pharmacokinetics were investigated in several different studies in healthy dogs, the majority of which were performed under GLP conditions, the conclusions of which are as follows:

- Although fluoxetine bioavailability was not studied after oral administration of the fluoxetine chewable tablets, a solution of fluoxetine HCL showed a bioavailability of 72 %.
- After administration of the racemate of fluoxetine, S-fluoxetine appears to have a larger systemic exposure than R-fluoxetine, whereas S and R-norfluoxetine exposure is similar.
- There is no statistical difference in the fluoxetine pharmacokinetic profiles between males and females.
- Levels of fluoxetine in plasma were below the LOQ by 24 or 48 hours post-dose.
- Food tends to enhance the rate and extent of fluoxetine absorption.
- After 21 days treatment with the recommended posology, there is accumulation of fluoxetine and norfluoxetine. Steady-state is reached after about 10 days.
- The kinetics are linear between 0.75 and 1.5 mg/kg.
- Norfluoxetine is the major metabolite.
- 7.19 % and 3.67 % of the dose was excreted in urine and faeces by 24 hours following dosing at 10 mg/kg of ^{14}C-fluoxetine.

The repeat dose toxicity studies were performed with fluoxetine capsules whereas the marketed formulation is chewable tablets. A study was therefore performed in healthy dogs to investigate the bio-similarity of fluoxetine capsules and chewable tablets. Bioequivalence analysis did not demonstrate bioequivalence of the two formulations on the basis of their AUCs as the confidence interval was just outside the limits but fluoxetine bioequivalence was confirmed on the basis of the Cmax. Concerning the metabolite norfluoxetine, bioequivalence was confirmed only on the basis of the Cmax. There is a carry-over effect for the AUC which invalidates the protocol and so bioequivalence analysis is not possible. Furthermore, due to the small number of dogs in the study there was probably not enough statistical power to demonstrate bioequivalence. A small correction for the dose also had to be made. In summary, although this bioequivalence analysis did not permit bioequivalence to be demonstrated between the two formulations, fluoxetine appeared to be more bioavailable from the tablet formulation than from the capsule formulation. However, the CVMP concluded that if a difference between the two formulations does exist, it is so small that it would have no clinical relevance.

Pharmacodynamics

All pharmacodynamic data are presented in section 4, Efficacy.

Toxicology

Single dose toxicity

Several studies had been performed in mice, rats, guinea pigs, cats, dogs and monkeys but most of these had been conducted in the 1970s (for the development of the human product) and were therefore not in compliance with current GLP principles. However, taking into account the number of studies and the different species and different modes of administration, the acute toxicity of fluoxetine was considered to be well characterised at dose rates in excess of the recommended dose for dogs (1 to 2 mg/kg bw).

Oral and intravenous studies in mice and rats showed the toxicity was much greater via the intravenous route.

Single oral doses of 100 mg/kg in dogs resulted in emesis, mydriasis, tremors and anorexia. Other species showed similar or less toxicity at that dose.

Acute toxicity studies have also been performed with the N-demethylated metabolite (norfluoxetine) by the i.v. and oral routes in mice and rats (i.v. only). The toxic effects of norfluoxetine seen were similar to those of fluoxetine.

The S- and R- enantiomers of fluoxetine hydrochloride were evaluated separately for their acute oral toxicity in mice and the results and signs of toxicity for each were similar to those of racemic fluoxetine hydrochloride.

Repeat dose toxicity

Several oral repeat dose toxicity studies were conducted with fluoxetine (as HCl) in mice, rats and dogs. Some were GLP compliant. Treatment periods ranged from 2 weeks to 12 months. The toxicological profile of fluoxetine is similar in laboratory animals and in the target species. Effects observed included tremors (dogs), anorexia and/or emesis and/or decreased weight gain (mice, rats, dogs), slow and/or incomplete pupillary response (dogs), mydriasis (dogs), hyperirritability (rats), aggressive behaviour (dogs), nystagmus (dogs), hypoactivity (dogs), ataxia (dogs), excessive urine output (rats), dose-related pulmonary histiocytosis (phospholipidosis or foam-cell reaction in the lungs) (mice, rats), phospholipidosis (mice, rats, dogs), slight changes in serum enzymes indicative of some liver toxicity (mice), liver fat deposition and lymphoid hyperplasia (rats), increased liver and kidney weights (rats). Hepatic fat deposition and lymphoid hyperplasia noted in all rat groups were not reversible.

In the target species, dogs, convulsions, tremors, slow or incomplete pupillary response, mydriasis, emesis, anorexia and phospholipidosis were the observed side effects at the recommended dose.

A dose-effect phospholipidosis was identified as a major toxicological effect of fluoxetine after chronic administration to dogs and was observed in the lung, liver, adrenals, lymph nodes, spleen and peripheral leukocytes in animals receiving the high dose. Phospholipidosis was only observed in the lung and leukocytes in the 1 mg/kg dose group. All effects observed in this study were reversible following a 2-month recovery period.

As some modified haematological parameters (increase of erythrocytes and packed cell volume and decrease of mean corpuscular haemoglobin concentration) were observed in one repeated dose study in mice, a study was performed in monkeys (in the 1970s) looking only at haematological parameters. Doses of up to 10 mg/kg bw were given orally for 14 days, then the animals were followed for a 14 day recovery period. Only a slight decrease in white blood cell count was observed in one treated female, which returned to normal during the recovery period.

Convulsions (seizures) were observed in one dog treated with 1mg/kg after weeks 15 of treatment and in one dog treated with 20 mg/kg after 9 weeks of treatment. This led to the inclusion of the following warning in section 4.5 of the SPC (and other product information) “Though rare, seizures may occur in dogs treated with Reconcile. Treatment should be stopped if seizures occur.”

Similar sides effects observed in the dog studies have been described in humans treated with fluoxetine. Many of the side effects appear to be associated with antimuscarinic effects.

Target species tolerance

There is no tolerance study with the final formulation. Reference was made to toxicological studies performed in dogs, especially a one-year chronic toxicity study and a biosimilarity study linking the final formulation and the formulation used in the one-year chronic toxicity study.

Reproductive toxicity

A fertility study in the female rat (GLP-compliant) and a single generation reproductive toxicity study in the rat (GLP-compliant) showed no adverse effects of fluoxetine (as HCl) treatment on a variety of reproductive parameters. Although the guideline recommends a 2-generation reproduction study, only a single generation reproductive toxicity study was performed. However, taking all the reproductive/developmental studies together, the CVMP considered the studies provided as sufficient although the Committee decided that a warning against using the product in breeding animals should be included in the SPC (section 4.7) "The safety of the veterinary medicinal product has not been established during pregnancy and lactation, thus the use is not recommended during pregnancy and lactation."

Two developmental toxicity studies were performed in the rat (non GLP-compliant) and rabbit (GLP-compliant). Although maternal toxicity was evident at high-dose rates, with a more pronounced effect in rabbits, no evidence of a teratogenic effect of fluoxetine was observed. NOELs for teratogenicity were above the RTD in the target species. Fluoxetine treatment was not associated with an increase in the incidence of malformations.

Mutagenicity

Both fluoxetine (as HCl) and the metabolite norfluoxetine were tested in bacterial mutagenicity studies, an *in vitro* rat unscheduled DNA synthesis study, cultured L5178Y mouse lymphoma cells and a Chinese hamster bone marrow *in vivo* sister chromatid exchange study. All the studies were conducted in compliance with GLP.

Fluoxetine and norfluoxetine did not exhibit any evidence of mutagenic potential in the battery of tests submitted which, it was noted, was not totally in agreement with VICH guidance. The VICH guidance (GL23) recommends for the *in vivo* test either a micronucleus test or a cytogenetics test. These tests evaluate the potential of a chemical to produce chromosomal effects whereas sister chromatid exchange test like unscheduled DNA synthesis evaluate primary DNA damage. However, the Committee concluded that taking into account the outcome of the submitted carcinogenicity studies, this was acceptable.

Carcinogenicity

Fluoxetine (as HCl) has been tested in GLP-compliant carcinogenicity studies in both mice (two studies) and rats (one study). The results showed fluoxetine not to be carcinogenic at daily oral doses of up to 11.5 mg/kg and 12.7 mg/kg for male and female mice respectively, and 8.6 mg/kg and 11.1 mg/kg for male and female rats respectively, after 2 years treatment.

Studies of other effects

Fluoxetine hydrochloride was evaluated for acute dermal, ocular and inhalation toxicity in rats and rabbits. The studies were GLP-compliant. No studies were performed with the final formulation. No skin irritation study or skin sensitisation tests were provided. Fluoxetine caused irritation to the eyes.

Observations in humans

Fluoxetine hydrochloride (Prozac) is well known in human therapy. The approved dose range is 20 to 80 mg/day. However, the use of doses as high as 320 mg/day have been reported in the medical literature without significant adverse consequences. Worldwide exposure to fluoxetine hydrochloride is estimated to be over 38 million patients. Review of databases of approximately 7,994 patients treated with fluoxetine or placebo in placebo-controlled clinical trials indicated that fluoxetine is generally well tolerated. Commonly reported side effects are wide and included nausea, asthenia, insomnia, somnolence, diarrhoea, tremor, dizziness, sweating, dry mouth, anorexia, yawn, decreased libido, urticaria and impotence.

User safety

The end user of these chewable tablet products is the small animal owner. The pharmaceutical form is a chewable tablet, so the main relevant route of exposure will be cutaneous contact during administration and the oral route in case of accidental ingestion.

According to toxicological data and post-marketing surveillance, a child weighing 10 kg would need to ingest 4 of the highest strength (64 mg fluoxetine) chewable tablets to reach a dose of 25 mg/kg. This dose is anticipated to cause serious illness or personal injury in at least 50% of children that have accidentally or deliberately ingested fluoxetine acutely and was derived from a database of post-marketing experience of 207 patients less than 18 years of age. As the packaging is a bottle with a child resistant closure it can be assumed that this event has a low probability.

Scenarios taking into account dermal contact for the animal owner were also considered by the applicant. The possibility of reaching toxic exposure levels by dermal absorption from handling Reconcile tablets was considered but concluded to be highly unlikely.

In summary, the user safety can be considered as good when the product is used as directed. The safety warnings included in the SPC were concluded as satisfactory.

Environmental safety

The environmental risk assessment stopped at Phase I. The product is for individual use in dogs only and the quantity used is small. Therefore, the risk to the environment from use of the product can be considered as very limited.

OVERALL CONCLUSION ON SAFETY

The pharmacokinetic data are satisfactory.

Although the toxicology data are from old, non-GLP studies performed for licensing of the human product, the Committee concluded from the number of studies provided, the different species and the different modes of administration, that the acute toxicity of fluoxetine had been adequately characterised at dose rates in excess of the recommended dose for dogs (1 to 2 mg/kg bw).

Fluoxetine is of low acute toxicity. The main adverse reactions in dogs following repeated administration of fluoxetine at the recommended dose were convulsions, tremors, slow or incomplete pupillary response, mydriasis, emesis, anorexia and phospholipidosis.

The S- and R- enantiomers of fluoxetine hydrochloride were evaluated separately for their acute oral toxicity in mice and the results were similar and the signs of toxicity were similar to those of racemic fluoxetine hydrochloride.

There was no tolerance study with the final formulation. Reference was made to toxicological studies performed in dogs and the Committee concluded this was acceptable given the battery of studies performed.

Only a single generation reproductive toxicity study was performed, however, taking into account all the reproductive/developmental studies submitted, the CVMP considered the studies provided as sufficient given the inclusion of a warning against using the product in breeding animals in the SPC. No further data were, therefore, required.

Two developmental toxicity studies were performed in the rat and rabbit. Although maternal toxicity was evident at high-dose rates, with a more pronounced effect in rabbits, no evidence of a teratogenic effect of fluoxetine was observed.

Fluoxetine and norfluoxetine did not exhibit any evidence of mutagenic potential in the battery of tests submitted. Although these were not totally in agreement with VICH guidance, the Committee concluded that taking into account the outcome of the submitted carcinogenicity studies, this was acceptable.

There was no evidence of carcinogenicity from the studies of fluoxetine in mice and rats.

Fluoxetine hydrochloride was not toxic via the skin, eye or inhalation routes. No skin irritation or sensitisation studies were reported but fluoxetine hydrochloride was found to cause eye irritation.

Fluoxetine hydrochloride (Prozac) is well known in human therapy. Potential routes of exposure to the user would primarily be by the dermal route and accidental oral ingestion. The user safety can be considered as good when the product is used as directed and the safety warnings included in the SPC were concluded as satisfactory. Useful information is given in section 4.5 of the SPC (Special precautions to be taken by the person administering the veterinary medicinal product to animals) in addition to the standard statement concerning accidental self-administration that "In humans, the most common symptoms associated with overdose include seizures, somnolence, nausea, tachycardia, and vomiting."

The environmental risk assessment (Phase I) has demonstrated that exposure of the environment to fluoxetine following the use of Reconcile chewable tablets will not be extensive. The environmental safety of Reconcile tablets is considered to be acceptable.

4. EFFICACY ASSESSMENT

Pharmacokinetics

This is reported under section 3, Safety.

Pharmacodynamics

Fluoxetine is a racemic mixture containing 50:50 R- and S-enantiomers. It has one demethylated metabolite, norfluoxetine, with R- and S-enantiomers. Although R-fluoxetine, S-fluoxetine and S-norfluoxetine have affinities for 5-hydrotryptamine uptake processes similar to racemic fluoxetine, R-norfluoxetine has a 15-fold lower affinity. All enantiomers of fluoxetine and norfluoxetine have relatively low affinities for norepinephrine and dopamine uptake, as does racemic fluoxetine.

The bibliographic documentation provided by the applicant shows that fluoxetine is a highly selective inhibitor of serotonin uptake, both *in vitro* and *in vivo*. As a result of inhibiting the neuronal uptake of serotonin released into the synaptic cleft, fluoxetine has a central effect by enhancing serotonergic neurotransmission in the brain and produces functional effects resulting from increased activation of serotonin receptors.

Fluoxetine inhibits catecholamine uptake only at high concentrations *in vitro* and has no effect on catecholamine uptake *in vivo* at doses that are used to inhibit serotonin uptake.

In contrast to many antidepressant drugs, fluoxetine lacks any significant affinity for neurotransmitter receptors, including the muscarinic cholinergic receptor, or α-adrenergic receptors, or histaminergic H1 receptors, and does not have direct effects on the heart. Also, fluoxetine does not act as a sedative.

Target animal safety

No tolerance study with the final formulation was provided, but long-term toxicity studies exist in the dog. These studies are reported under section 3, Toxicology, Repeat Dose Toxicity. A bioequivalence study was performed between the chewable tablet and the capsule used in the toxicological studies. Fluoxetine is more bioavailable from the tablet than from the capsule.

EFFICACY STUDIES:

Field trials

For the demonstration of the efficacy of fluoxetine against Separation Anxiety (SA) in dogs, four GCP field studies were submitted: one dose-determination study; one placebo-controlled study combined with behaviour modification; one placebo-controlled study without behaviour modification; and one non-inferiority study. All dogs were client-owned.

The first study was a **dose determination study**. This was an EU multi-centre randomised, double-blinded, placebo-controlled, parallel group field study performed without behavioural modification therapy. Dogs enrolled were more than 6 months old, neither pregnant nor lactating and showed at least one of the following separation anxiety behaviours, within an eliciting context involving the absence of the owner at least 50% of the time: inappropriate urination; inappropriate defecation; destructive behaviours (including re-arranging behaviours); excessive salivation; excessive licking or grooming; excessive vocalisation; shaking or shivering; restlessness; appearing depressed. Dogs were randomly allocated to one of five treatment groups and given fluoxetine (as the marketed formulation) at one of four different dose levels (0.25-0.5 mg/kg/d, 0.5-1.0 mg/kg/d, 1.0-2.0 mg/kg/d, and 2.0-4.0 mg/kg/d) or placebo, once per day for 56 days, orally, either with or without food. The nine individual behavioural signs of separation anxiety described above were subjectively scored by the owners every

two weeks. The owners also provided a single subjective global score reflecting their overall perception of their dog's behaviour.

The results showed that the proportion of dogs with improved scores generally increased over time in all the treatment groups, except in the 2-4 mg/kg/d group where it remained stable from day 29 onwards, and in the 1-2 mg/kg/d group where it decreased between day 43 and 57. By the end of the study, the placebo and all doses were comparable, however a higher proportion of dogs in the fluoxetine groups improved more quickly compared to the placebo group. Except on day 57, this treatment effect appeared to occur in a dose-related manner.

Eight weeks post-treatment, a last telephone interview was made and information was obtained for many dogs on the evolution of the global behaviour score. For all treatment groups the score was mild to moderate in the previous two weeks, and unchanged to slightly improved compared to the end of the treatment, except for the 1-2 mg/kg/d treatment group, for which it was unchanged compared to the end of the treatment.

The overall rate of adverse events in the safety population during the treatment period was between 2.99% and 3.07% in the placebo and two lower dose groups, but 4.07% and 4.91% in the 1 – 2 mg/kg and 2 – 4 mg/kg dose groups respectively. The observed side-effects of treatment with fluoxetine are decreased/loss of appetite, lethargy, muscle tremors, constipation and mydriasis. At the highest dose of 2-4 mg/kg, observed side-effects of decreased/loss of appetite and lethargy were the signs most frequently recorded. The incidence of muscle tremors is undesirably high and more severe in comparison to the lower doses. Mydriasis is limited to the highest dose of 2 - 4 mg/kg.

CVMP noted that a dose determination study under controlled conditions with at least one quantitative parameter would have been preferred, rather than this field study with subjective owners' scoring. However, the results from this study show that there is a dose-related treatment effect in the first weeks of treatment, although it cannot be distinguished from the placebo at the end of the treatment. Eight weeks after treatment, there does not appear to be much difference between the placebo and treatment groups. The rate of adverse events is similar in the placebo, 0.25-0.5 and 0.5-1.0 mg/kg/d groups, but higher in the 1 - 2 and 2 - 4 mg/kg/d groups.

Studies two and three were **dose confirmation studies**. One study was performed with behavioural modification and the other without.

Study two was a non-EU, multi-centred, placebo-controlled, double-blinded, parallel-arm GCP study. The dogs enrolled were more than 6 months old, neither pregnant nor lactating and were showing at least one of the nine separation anxiety behaviours. They were randomly allocated in two groups and received either fluoxetine chewable tablets orally at a dose of 1 - 2 mg/kg/day for 56 days or placebo. All dogs received behaviour modification therapy. The efficacy criterion was the incidence of dogs demonstrating improvement in the owner-provided overall severity score for separation anxiety behaviour.

On the first visit of the animal owner and dog with the investigator, up to four individual separation anxiety behaviours were identified. The dog owners then assigned severity scores for the dog's separation anxiety behaviour at the end of each week. At the end of week 2, the investigator assessed the results and assigned the dog to one of two treatment routines. Then, after 56 days of treatment, the data recorded by the dog owner and the dogs themselves were reassessed by the investigator.

Seventeen percent of the dogs given placebo combined with behaviour modification improved within one week of treatment initiation. When fluoxetine was combined with behaviour modification, approximately 42% of the dogs improved within one week of treatment initiation, which is significantly more than those in the placebo group.

The fluoxetine-treated group continued to have a higher incidence of improvement over the course of the treatment period and by the end of the 8-week treatment period, approximately 72% of the fluoxetine-treated dogs had an improved global severity score of 50%.

Dogs were not evaluated beyond 8 weeks, therefore, it was not possible to conclude on the long term outlook for dogs where treatment is continued with behaviour modification alone.

In general, fluoxetine was significantly more effective than placebo in increasing the incidence of improvement in severity score for destructive behaviour, excessive vocalisation and restlessness, with the exception of week 1 for excessive vocalisation and week 3 for destructiveness.

The use of owner derived global assessment scores for scoring the separation anxiety was validated for the assessment of improvement and no change, with the scoring tending to overestimate any deterioration.

The overall adverse events rates reported showed a differentiation between those reported by the owners and by the investigators. There was a significant increase in the following treatment-emergent adverse events for dogs administered fluoxetine: excessive vocalisation (including whining), lethargy/increased sleeping and decreased appetite. Four serious adverse events were reported in this study: three seizures in fluoxetine-treated dogs (10 days, 45 days and 6 months following the last dose of fluoxetine) and one in placebo-treated dogs.

This well-conducted pivotal efficacy study showed that the oral administration of 1-2 mg/kg of fluoxetine once daily was effective for the treatment of separation anxiety in dogs when administered in conjunction with behaviour modification therapy. Given the higher level of adverse reactions (lethargy, anorexia, tremor, vomiting, restlessness and excessive vocalisation) in the fluoxetine-treated group compared to the placebo group, particularly the level of serious adverse events, appropriate warnings were included in the product information not to exceed the recommended dose.

Study three was identical to study two except that none of the dogs received any behaviour modification therapy, and so received either fluoxetine (at 1 – 2 mg/kg in the form of chewable tablets) or placebo. Additionally a secondary efficacy criterion was used, which was the frequency of separation anxiety behaviour relative to the number of departures of the dog owner.

In the primary analysis of the efficacy evaluable population, the incidence of improved global separation anxiety scores was significantly greater during treatment weeks 1 and 4 for fluoxetine-treated dogs compared to dogs receiving placebo. The difference during the other treatment weeks was, however, not statistically significant.

There was a significant increase in the following treatment-emergent adverse events for dogs administered fluoxetine: anorexia; decreased appetite; and, lethargy/depression. The emergence of anorexia and decreased appetite in the fluoxetine-treated dogs may have contributed to their weight loss over the 42-day treatment period. Whereas placebo-treated dogs gained 0.15 kg weight on average, fluoxetine-treated dogs lost 0.29 kg. There were two serious adverse events reported in this study: one seizure in a fluoxetine-treated dog 9 days following fluoxetine administration, and one seizure in a placebo-treated dog.

The results of this study show that after four weeks of treatment, the efficacy of fluoxetine is lower when administered without behaviour modification therapy than with it. The adverse effects are higher for the treatment group than for placebo, are mostly anorexia and decreased appetite, leading to a significant weight loss in the fluoxetine-treated group.

This study showed no overall statistical improvement in separation anxiety. Thus the study is only suitable for demonstration of the safety of Reconcile.

From these two dose determination studies it can, therefore, also be concluded that, when compared to placebo, the efficacy of Reconcile is higher when behavioural modification therapy is also used.

The fourth study was an EU **clinical field trial** which was a multi-centred, randomised, positive-controlled, double-blinded, parallel-group GCP study. The dogs enrolled showed at least one separation anxiety behaviour and were randomly allocated one of two groups, to receive either fluoxetine or clomipramine. In addition all dogs received behavioural training. All the animals were more than 6 months old, neither pregnant nor lactating. The two treatment groups received either fluoxetine orally (as the chewable tablet) at a dosage of 1 - 2 mg/kg/day for 56 days, or clomipramine capsules orally at a dosage of 1 - 2 mg/kg twice daily for 56 days, in conjunction with behavioural modification therapy.

The primary efficacy criterion was a comparison of global severity scores to examine non-inferiority between the two treatments during 8 weeks of treatment. A 20% point difference in separation anxiety behaviour improvement rate was regarded as the equivalence margin. Secondary outcome measures related to a comparison of scores for individual behaviours, frequency of separation anxiety signs and time to improvement. Comparisons between the two treatments were also made during a 6 week follow-up period following the cessation of treatment.

Non-inferiority was statistically achieved at every interview throughout the treatment. At the end of the treatment phase, the fluoxetine group provided significantly better treatment responses with regards to inappropriate defecation and destructive behaviour. At the end of the post-treatment follow-up phase, however, the clomipramine-treated group exhibited significantly better treatment responses with regard to destructive behaviour and excessive salivation.

A number of separation anxiety behaviours were not improved significantly by treatment with either fluoxetine or clomipramine; these were excessive salivation, excessive licking/grooming, shaking or shivering and apparent depression.

The rate of relapse at the end of the post-treatment phase was higher (around 28%) in the fluoxetine-treated group compared to the clomipramine-treated group (relapse rate of around 23%).

No significant difference between treatment groups was seen in the number or type of adverse events recorded during either treatment or post-treatment. A small proportion of individual separation anxiety behaviours appeared to worsen for both treatment groups and during both the treatment and the post-treatment phases.

The results of this clinical field study show the non-inferiority of fluoxetine in the treatment of separation anxiety compared to a reference product (clomipramine) when given in conjunction with behavioural therapy.

OVERALL CONCLUSION ON EFFICACY

The pharmacodynamic data are satisfactory. Fluoxetine is a highly selective inhibitor of serotonin uptake, both *in vitro* and *in vivo*, and lacks any significant affinity for neurotransmitter receptors, including the muscarinic cholinergic receptor, or α-adrenergic receptors, or histaminergic H1 receptors, and does not have direct effects on the heart. Fluoxetine does not act as a sedative.

There was no tolerance study with the final formulation. Reference was made to toxicological studies performed in dogs and the Committee concluded this was acceptable given the battery of studies performed.

Reconcile chewable tablets showed a significant improvement in treated dogs on their vocalisation and inappropriate defecation and/or urination, but only when used in conjunction with behavioural modification, and this was reflected in the SPC and product literature.

All four efficacy studies had a limited treatment duration (maximum of 8 weeks) and this is adequately reflected in the SPC section 4.9 (Dose and Method of Administration). No data were provided to support an indication for the long-term use of Reconcile for treating separation anxiety in dogs,

however, the CVMP noted that the overall tolerance profile was deemed satisfactory and there was no specific indication in the dossier that continued treatment beyond 8 weeks would not be beneficial. The Committee went on to note that long term use of the product might be encountered in the field and agreed that such long term use (where the product is used in combination with behaviour modification therapy as indicated in the SPC and product literature) could be left up to the discretion of the attending veterinarian as clear advice was included in section 4.9 of the SPC : "Clinical improvement with Reconcile tablets is expected within 1 to 2 weeks. If no improvement is noted within 4 weeks, case management should be re-evaluated. Clinical studies have shown that a beneficial response has been demonstrated for up to 8 weeks treatment with fluoxetine."

The overall tolerance profile from the four clinical studies was in line with what was expected after the chronic toxicity studies in dogs.

5. BENEFIT RISK ASSESSMENT

Reconcile chewable tablets contain fluoxetine and are indicated as an aid in the treatment of separation-related disorders in dogs manifested by destruction and inappropriate behaviours (vocalisation and inappropriate defecation and/or urination) and only in combination with behavioural modification techniques. Behavioural modification therapy is the most important part of therapy and the field use of such a product is justified by a more speedy recovery of the animal patient.

The active substance, fluoxetine, has been authorised as a medicinal product for human use for approximately a decade and has been very widely used. It has also been the subject of a European Pharmacopoeia monograph for quite some time. The quality of the Reconcile chewable tablets is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way and take account of the relevant current European and VICH guidance. There are no unresolved quality issues which have a negative impact on the benefit : risk balance of the product.

The pharmacokinetics of fluoxetine have been sufficiently described.

Fluoxetine is of low acute toxicity. A number of studies investigated repeated administration of fluoxetine (as HCl) in both the target and non-target species. These demonstrated that the toxicological profile of fluoxetine is similar in laboratory animals and dogs. The main signs of toxicity are side effects on the nervous system like ataxia, tremors, anorexia and metabolism perturbations with phospholipidosis. In the target animal, dogs, side effects as convulsions, tremors, slow or incomplete pupillary response, mydriasis, emesis, anorexia and phospholipidosis were observed at the recommended dose. Similar side effects are described for the dog as have been described in humans in the literature. Many of the side effects appear to be associated with antimuscarinic effects. In the absence of any target species tolerance study with the final formulation the Committee agreed that adequate data were available from the wealth of data available in all the toxicological studies.

Data on reprotoxicology are limited, but as the product is contra-indicated during pregnancy and lactation the Committee concluded that no further data were required.

Fluoxetine did not show any mutagenic, carcinogenic or teratogenic activity.

In terms of user safety, the active substance fluoxetine and the excipients do not pose any particular risk to the user and appropriate user safety warnings are included in the SPC and product literature. Fluoxetine is also widely used in human medicine.

The product is only used in companion animals. A Phase I Environmental Impact assessment was performed following current guidelines, considered acceptable and the applicant exempted from any further calculation regarding environmental risk assessment.

Fluoxetine has been shown to be a highly selective inhibitor of serotonin uptake, both *in vitro* and *in vivo*, and the pharmacodynamic data are satisfactory.

In terms of target animal safety and efficacy, it is noted that the administration of fluoxetine to dogs at the recommended dose (1 - 2 mg/kg) is expected to cause a number of adverse events ranging from lack of appetite (very common) to seizures (very rare). However, all the adverse events appear linked to the mechanism of action of the active substance and are mentioned explicitly in the SPC and product literature.

Reconcile chewable tablets showed a significant improvement in treated dogs on their vocalisation and inappropriate defecation and/or urination, but only when used in conjunction with behavioural modification, and this was reflected in the SPC and product literature.

All four efficacy studies had a limited treatment duration (maximum of 8 weeks) and this is adequately reflected in the SPC section 4.9 (Dose and Method of Administration). No data were provided to support an indication for the long-term use of Reconcile for treating separation anxiety in dogs, however, the CVMP noted that the overall tolerance profile was deemed satisfactory and there was no specific indication in the dossier that continued treatment beyond 8 weeks would not be beneficial. The Committee went on to note that long term use of the product might be encountered in the field and agreed that such long term use (where the product is used in combination with behaviour modification therapy as indicated in the SPC and product literature) could be left up to the discretion of the attending veterinarian as clear advice was included in section 4.9 of the SPC: "Clinical improvement with Reconcile tablets is expected within 1 to 2 weeks. If no improvement is noted within 4 weeks, case management should be re-evaluated. Clinical studies have shown that a beneficial response has been demonstrated for up to 8 weeks treatment with fluoxetine."

The application for Reconcile therefore strikes a balance between the risks associated with use of the product and the benefits that can be expected from use of the product in the indication of separation anxiety in dogs where behaviour modification therapy is also instigated and maintained. The benefit: risk balance is therefore deemed to be favourable.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EEC as amended.