SCIENTIFIC DISCUSSION

1 SUMMARY OF THE DOSSIER

Slentrol oral solution for dogs contains dirlotapide 5 mg/ml as the active substance. The active substance of Slentrol, dirlotapide, is a potent inhibitor of the microsomal triglyceride transfer protein (MTP). It works locally in the intestine by inhibiting the transfer of lipids into the bloodstream which indirectly produces an appetite suppressant effect. The benefits of Slentrol are its ability to reduce bodyweight in adult dogs when given in accordance with the approved treatment schedule, until the target body weight is reached. The treatment is given once daily directly into the mouth or on a small amount of food. The product can be administered with or without food.

The most common side effects are one or more vomiting events, sometimes accompanied by signs of tiredness, disinterest in food or diarrhoea, which can reoccur occasionally during the course of treatment. The approved indication is: "As an aid in the management of overweight and obesity in adult dogs. To be used as part of an overall weight management programme which also includes appropriate dietary changes and exercise practice."

2. QUALITY ASSESSMENT

Composition

Slentrol oral solution contains 5 mg/ml dirlotapide as active substance. The only excipient is medium chain triglyceride (MCT) oil.

Container

Dirlotapide oral solution (5 mg/ml) is presented in 20 ml, 50 ml and 150 ml white polypropylene (PP) bottles fitted with a low density polyethylene (LDPE) bottle adapter. The bottles are closed with a child resistant (CR) closure. The system is suitable to protect the medicinal product from light exposure. Each bottle will be supplied inside an outer carton with an appropriate number of 1 ml, 3 ml or 10 ml oral dispensing devices respectively. The oral dosage devices are CE marked and meet the specifications for a Class 1 device with measuring function. When first fitted into the bottle adapter, the tip of the oral dosing device will tear the broachable membrane.

Studies have been performed to establish the compatibility, safety and performance of the proposed container closure system and oral dosing devices. The specifications for the packaging components comprise tests for identity (code number), physical characteristics (e.g. colour and dimension). Compliance with Directive 2002/72/EC relating to plastic materials intended to come in contact with foodstuffs was shown, which provides reassurance in relation to quality.

Clinical Trial Formula(e)

The formulation has remained unchanged throughout the development of the drug product, except for one safety study where the strength was 10 mg/ml but is identical to the proposed commercial formulation. Only the container closure systems have differed.

Development Pharmaceutics

Dirlotapide active substance is a white to pale pink coloured powder which is practically insoluble in water. Therefore an oily excipient was chosen for the formulation. The particle size of dirlotapide has no impact on the manufacturing parameters or product characteristics of the oral solution, thus no particle size criterion has been set. During early development other solvents were investigated as suitable vehicles, due to the poor solubility of dirlotapide in water. Medium chain triglyceride was acceptable and is listed in the Ph.Eur. It is precedented as a dietary supplement in enteral nutrition and commercially available to pharmaceutical standards. The in-house standard for the chosen excipient is

narrower than the Ph.Eur. monograph regarding the fatty acid chain lengths distribution and water content.

No preservative has been included in the formulation as studies have demonstrated that it does not support microbial growth and the product quality is maintained throughout repeated use (the product meets the requirements of the Ph.Eur. 'Efficacy of antimicrobial preservation' test). A limit for water content has been established to ensure that a separate water phase does not occur in the medicinal product. Stability data in the proposed commercial packaging and in glass bottles with polypropylene closures demonstrate that dirlotapide oral solution is chemically and physically stable when stored below 30°C. No overages are used in the manufacture of the medicinal product.

Conventional equipment and standard processing techniques are utilised in the manufacture of the medicinal product. No critical steps were identified requiring in-process controls for the manufacturing process. The batch analysis data demonstrate that the manufacturing process produces a medicinal product of consistent quality. The only issue identified during the manufacture of the stability batches was product leakage from a number of bottle adapters prior to cap application. The manufacturer has corrected the air removal during the moulding process and the problem is no longer observed. The bottle adapter design has been developed to optimise the effectiveness of the container seal and incorporate a broachable membrane at the base of the dosing hole which will be fitted into the bottleneck as part of the commercial manufacturing operation. It is intended that the membrane will be broached at first dose withdrawal and the adapter will be left in position through the 'in-use' period. Good seal integrity has been demonstrated at a range of storage conditions.

Method of Manufacture

A manufacturing formula for the proposed batch size was presented. This product is a true solution and is produced using conventional equipment and standard processing techniques. The manufacturing process is a standard process comprising solution preparation, filtration and filling. The temperature of the excipient medium chain triglyceride (MCT) oil has been identified to be of importance to the dissolution speed and is defined in the manufacturing process. Three full scale validation batches have been manufactured and tested to define and underwrite the operating limits for all the manufacturing parameters on the proposed commercial manufacturing equipment. All operating limits, including dissolution temperature and time, will be controlled through the batch manufacturing record and all critical attributes of the drug product will be tested at the final product stage and controlled through the finished product specification. A detailed validation protocol for full-scale batches for the medicinal product was provided.

Control of Starting Materials

Active Substance

Dirlotapide ($C_{40}H_{33}F_3N_4O_3$) is not detailed in any pharmacopoeia and a detailed specification was provided including tests for appearance, identity, loss on drying, residue on ignition, impurities and assay. The absence of tests for microbiology, solid form and particle size have been justified. The proposed specification limits are based on analysis of batches manufactured by the proposed commercial synthesis and on stability results.

Flow charts of each step of the synthesis as well as descriptions of the manufacturing process are provided. The manufacturing process is described as a three step chemical process. Satisfactory specifications for starting material, intermediates, catalysts, reagents and solvents are provided. Impurity specifications have been justified by batch history and by demonstrating the fate of impurities during synthesis.

The unspecified impurity limit is based on the VICH identification thresholds. The limit for total impurities is based on the summed limits for individual impurities. This was considered appropriate based on the limited number of batches that have been made to date using the proposed commercial process and also on the limited experience of manufacturing at scale to date.

The limits for residual solvents (all class 3) are based on the general VICH GL 18 limits. All other solvents used in the manufacture of the proposed starting materials would be detected by the analytical procedure and a limit for individual Class 2 solvents has been established for dirlotapide active substance.

A description of physico-chemical characteristics of the drug substance was presented (pKa, melting point, polymorphism, solubility etc.). The structural elucidation has been carried out by elemental analysis, IR, ^{1}H -NMR, ^{13}C -NMR, ^{19}F -NMR and MS. Dirlotapide has been shown to exist as 17 crystalline forms as identified by powder X-ray diffraction (PXRD). Dirlotapide form A, an anhydrous form, was selected to be the solid dosage form used in the commercial manufacture of the medicinal product. Form A is chemically and physically stable. It is reproducibly produced by the proposed commercial process.

Batch data from the proposed manufacturing site confirm satisfactory uniformity and compliance with the specification and demonstrate that active substance of the desired quality can be consistently produced.

Stability testing included: appearance, assay, impurities, water content, solid form identity by PXRD, and microbial purity (Ph.Eur. 5.1.4). No trends were seen regarding assay, related substances, enantiomeric purity, X-ray diffraction, water or microbiological quality. Two unspecified impurities were reported at release and remained at the same level throughout the study. The photostability study conducted according to VICH GL5 did not result in any significant changes in any stability indicating parameters. A retest period of 2 years and no special storage conditions for the active substance was agreed.

Excipients

A specification is set for medium chain triglyceride oil, the only excipient used in the veterinary medicinal product. This conforms to the Ph.Eur. monograph, but the specification limits for fatty acid composition and water are narrower than those of the Ph.Eur. Typical certificates of analysis for MCT oil that meets the requirements of the Ph.Eur. and in-house requirements were presented.

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

A declaration is provided stating that all the components used in the manufacture of Slentrol comply with Directive 1999/104/EC and the current TSE guideline (EMEA/410/01-Rev. 2). No materials of animal origin are contained or used in this veterinary medicinal product.

Control Tests on the Finished Product

Specifications and details of routine tests for control of Slentrol finished product including appearance, identity of the active, assay, fill volume, individual and total degradation products and water content were provided. The absence of tests for chiral identity and purity is justified based on the control of the drug substance and stability data on the medicinal product. The absence of a test for microbial integrity is justified since the veterinary medicinal product does not support microbial growth and also by in-use tests of the stability studies. The absence of a test for Uniformity of mass of delivered doses from multidose containers was also justified. It is considered that tests for the degree of colouration, density and viscosity are not indicative of the quality of dirlotapide oral solution. These attributes are controlled through the specification for the excipient, MCT oil. The delivery of the required dose of dirlotapide oral solution, 5 mg/mL, is a function of the dosing device.

Details of all test procedures and analytical methods were provided. The HPLC method for determination and identification of the active substance and determination of related substances has been satisfactorily validated in line with VICH requirements.

The batch data complies with the specification for the assay, total degradation products and water content. Batch analysis data from batches manufactured with the commercial formulation are presented which support the validity of the manufacturing method and the robustness of the formulation.

Stability Tests on the Finished Product

Stability data of batches, including testing in both upright and inverted positions have been provided. Parameters tested include: appearance, assay, individual unspecified degradation products, total degradation products, water content, chiral purity (bracketing employed) and microbial quality (bracketing employed). No significant changes to or any trends for the parameters tested occurred in the stability study, the degradation products (including the enantiomer) remained below the limit set. Since the product is stable under all storage conditions, extrapolation to two years shelf life was accepted with no special storage conditions. Photostability studies demonstrated that the drug product is stable to light exposure in the proposed commercial packaging material and temperature cycling studies demonstrated that the product is stable under short term excursions of the temperature. Bracketing has been employed with the largest and smallest pack sizes fully tested and the midsize package reduced tested.

Further confirmatory stability data from production scale batches from the manufacturing site on accelerated (40°C/75% RH) and long term (30°C/65% RH) stability programmes will be provided. A shelf-life of 2 years without storage restrictions, except that the product shall be stored in the original container, was accepted.

In-use Stability Tests

In-use stability testing did not show any tendency towards degradation or any other changes in the product. All results remain within specification. An in-use shelf-life of 3 months was supported based on the data provided.

OVERALL CONCLUSION ON QUALITY

Slentrol oral solution 5 mg/ml for dogs contains the active substance dirlotapide and is presented as a non-aqueous solution containing medium-chain triglyceride oil as the only excipient. The product is presented in 20 ml, 50 ml and 150 ml white polypropylene bottles with a bottle adapter. Two oral dosing devices are supplied with each bottle. Dose accuracy has been demonstrated.

The solution is manufactured using a standard manufacturing process involving dissolution of the active substance in the solvent. Process validation has been carried out on pilot scale batches. The manufacture of the active substance, in a three step process from three starting materials, is described in detail. The only impurity (the enantiomer) found above VICH qualification limits has been qualified in toxicological studies. The proposed specification has been justified and impurities are controlled in line with VICH Topic GL10.

The product specifications include tests for active substance content and identity, chromatographic purity, water content and fill volume. Analytical methods and validation for the veterinary medicinal product are generally considered acceptable and in line with VICH GL 2. Batch data for several batches are in accordance with the specification.

The shelf life specifications for the product are the same as for release. Stability data under VICH conditions has been presented for three pilot scale batches of product packed in the packaging proposed for marketing. It has been demonstrated that changes in stereochemical purity do not occur on storage. A shelf-life of 2 years without storage restrictions except that the product shall be stored in the original container as it is light sensitive, was approved. An in-use shelf-life of 3 months was agreed.

3. SAFETY ASSESSMENT

Pharmacology

Several studies concerning the safety pharmacology of dirlotapide were conducted.

Dirlotapide produced no neurofunctional effects and did not affect pulmonary or renal function in rats up to a dose of 50 mg/kg. However, due to the low bioavailability of dirlotapide, the systemic exposure obtained in rats was below what is observed in dogs administered the highest recommended clinical dose (1 mg/kg/day). No relevant cardiovascular effects were noted in radio-telemetry-instrumented dogs at doses up to 25 mg/kg, which corresponds to a 3-fold exposure margin when based on C_{max}. Dirlotapide did not inhibit the hERG current at a testing concentration of 10 µM. It is concluded that CNS, CV, pulmonary, or renal safety pharmacology issues are unlikely following therapeutic use of dirlotapide.

Pharmacokinetics

Since dirlotapide acts locally and since no PK/PD relationships has been established for any endpoint, systemic exposure is not required for efficacy but may be relevant to some toxicological endpoints. At the time that the assay method for the determination of dirlotapide in dog plasma was being developed and validated, it was noted that, while dirlotapide often could be detected in samples at very low concentrations, the Lower Limit of Quantification (LLOQ) was established at 5 ng/mL. While the LLOQ of 5 ng/mL did not permit accurate pharmacokinetic characterisation in the target species for doses at the lower end of the therapeutic range, further method development work to reduce the LLOQ was not performed since the method provided sufficient data for target animal safety and toxicological studies.

The intravenous and oral pharmacokinetics, the effect of food on oral exposure and the oral dose linearity of dirlotapide 5 mg/ml after single administration were all investigated in studies. Following IV administration dirlotapide exhibited multi-exponential pharmacokinetics. There was large inter-animal variability but no apparent differences between males and females.
Following oral administration plasma concentration profiles were characterised by low C_{max} and concentrations that declined quickly below the assay LLOQ. In general, T½ values from oral doses were similar to those following IV doses. The variability in AUC was large (> 30% CV).
Oral bioavailability (F) was calculated using $AUC_{0\text{-}inf}$. Since extrapolation was greater than 30% in many animals in the 0.05 and 0.3 mg/kg groups, oral bioavailability was thus underestimated for several animals.

AUC and C_{max} values increased with increasing dose, however neither AUC_{last} nor C_{max} were dose proportional between 0.05 and 1.0 mg/kg. Interpretations about dose linearity are complicated by the lack of plasma concentration data for several animals in the lowest dose group, use of AUC_{last} values which underestimated areas under the curve for several animals and large inter-animal variability. However, there is a tendency for an increase of AUC/dose vs dose.

To assess the effect of food upon dirlotapide pharmacokinetics, PK parameters were compared for the 0.3 mg/kg PO-fed and 0.3 mg/kg PO-fasted groups. T_{max} and C_{max} were not affected by presence or absence of food. Overall drug exposures based upon mean AUC_{last} and $AUC_{0\text{-}inf}$, were approximately 1.5x higher in fed than fasted animals.

There were recorded differences between the sexes. However, the differences were minor and should be interpreted with caution due to the large variability and the difficulties in estimating the AUC.

Due to large variability and the relatively high lower limit of quantification, the pharmacokinetics could not be characterised in detail. However, the single dose PK data are sufficient. As Slentrol acts locally, the systemic exposure is of potential relevance for safety but not for efficacy.

A study to determine the distribution, metabolism, and excretion profile of dirlotapide in healthy beagle dogs was conducted. The results are in agreement with the data recorded from the other PK studies. However, as the limit of determination of the assay is lower in this study the plasma profile could be followed over a longer time period. The non-linear elimination phase (on a semi-logarithmic scale) is clearly evident. The terminal slow elimination phase seems to cover a rather large part of the AUC and could therefore at least partly explain the high accumulation index after once daily treatment.

The radiolabelled mass balance and routes of excretion of [^{14}C]dirlotapide following single oral administration of a high dose were determined in a study. Measurable levels were detected in the plasma and blood of all dogs up to the 168 h time point. Approximately 80% and 73% of the dose was recovered in the faeces of male and female dogs, respectively within 48 h of dose administration.

The documentation of the pharmacokinetic characteristics of dirlotapide is limited by the bioassay. The lower limit of quantification was high and therefore the half-life and accumulation index are poorly defined. From the data available it can be concluded that the pharmacokinetics are complex with formation of a large number of metabolites. The initial elimination is rapid followed by several slower phases. It seems as if the bioavailability increases with dose and there is a prominent food interaction with higher bioavailability under fed conditions. As dirlotapide acts locally, the pharmacokinetics are of interest for the tolerance aspects only. No PK/PD relationships have been established for any endpoint.

Due to the altered absorption of fat, dirlotapide could potentially interact with other drugs, especially lipid soluble compounds whose rate and extent of absorption might be affected. However significant interactions regarding the rate and extent of absorption of fat soluble drugs are unlikely since inhibition of the absorption of fat soluble compounds is partial, being reduced by an average of about 10% by comparison with untreated animals. Furthermore, the risk for pharmacokinetic drug interactions following dirlotapide co-administration with CYP3A substrates/inhibitors/inducers was addressed. In the SPC section 4.8 it is stated that interaction studies have not been performed. Therefore, for dogs receiving treatments in addition to the product, drug interactions should be monitored closely.

Toxicological studies

Single dose toxicity

The acute oral toxicity of dirlotapide was evaluated from first dose effects in repeat-dose studies in rats and dogs. No mortality or clinical signs were observed at oral doses up to 200 mg/kg in rats. No mortality was observed at oral doses up to 10 mg/kg (MCT vehicle) in dogs.

The acute dermal toxicity was evaluated in the rat in accordance with the OECD Guideline 402 Acute Dermal Toxicity and the Commission Directive 92/69/EEC. Dirlotapide, at a dose of 2000 mg/kg was applied to skin and then covered with a semi-occlusive patch for 24 hours. Observations were made at 0.5, 1, 2, and 4 hours after the patch was removed; then daily for 14 days. No mortality, signs of systemic toxicity, signs of dermal irritation, bodyweight changes, or gross abnormalities at necropsy were noted. The acute dermal LD_{50} of dirlotapide was > 2000 mg/kg.

No oral single-dose toxicity studies were performed. In general, the single-dose toxicity studies should be performed in order to evaluate the acute toxic effects and the time course for their onset and remission. However, given the overall low toxicity of dirlotapide, almost exclusively related to the pharmacological action and secondary effects from prolonged fasting, the lack of specific single-dose toxicity studies was deemed acceptable.

Repeated dose toxicity

A number of GLP and non-GLP repeat-dose toxicity studies were conducted in rats and dogs (the target species). The main findings in the rat studies were lipid accumulation in small intestinal

enterocytes and hepatocytes, correlating with increased liver weights, which are all expected findings when considering the pharmacological mechanism of dirlotapide. In rats, treatment related changes in serum chemistry parameters were noted for ALT, ASP, ALP, globulin, A/G ratio, cholesterol and glucose. The magnitude of the changes appeared to exhibit a dose relationship, with changes at 50 mg/kg/day and 200 mg/kg/day being generally similar. Systemic exposure did not increase for doses ≥ 50 mg/kg/day. In a 3-month study, effects on fat-soluble vitamins (A, D, E, and K) were monitored in serum and various tissues. Mean serum vitamin E levels were decreased at ≥ 1 mg/kg/day in a non-dose related manner. However no apparent changes were noted when normalised for reduction in total lipid concentration. Following 1-month recovery mean serum and tissue vitamin levels were comparable to controls. Increased liver weights, pale livers, pale mucosal surface in the small intestine correlating with vacuolation of hepatocytes and enterocytes were observed. In rats, the achieved systemic exposure at the highest dose of 50 mg/kg/day was lower than the exposure observed in a single-dose PK study in dogs administered dirlotapide at the maximum recommended clinical dose of 1 mg/kg.

In dogs, toxicity was manifested as increases in serum AST and ALT at doses ≥ 1.5 mg/kg/day. This correlated with minimal hepatic single-cell necrosis at doses ≥ 10 mg/kg/day in the dose-range finding study only. Other findings were effects consistent with the pharmacological action of a microsomal triglyceride transfer protein (MTP) inhibitor (bodyweight loss, decreased serum lipids, decreased serum vitamin A and E, lipid accumulation in enterocytes, hepatic lipid accumulation, increased liver weights and associated inflammatory responses) as well as secondary effects (e.g. decreased lipid absorption) similar to effects expected from prolonged fasting. Haematology findings were changes in erythrocytic parameters, changes in erythrocyte morphology (burr cells, possibly secondary to low cholesterol levels) and increases in platelet counts. Toxicological findings were serum elevations of ALT, AST, and GDH. Atrophy of cortical thymus was observed and correlated with reduced thymus weights at doses ≥ 2.5 mg/kg/day. Atrophy of cortical thymus was also observed in control animals and there were no differences in degree between control and treated animals. Following 1-month recovery generally all treatment related changes at 25 mg/kg/day had returned or were returning towards control levels. Based on the marked elevations in hepatic enzymes and reductions in body weights at doses ≥ 2.5 mg/kg/day the 0.25 mg/kg/day dose level was identified as a NOAEL. The NOAELs derived from the 3-month rat study and the 3-month dog study were 1 mg/kg/day and 0.25 mg/kg/day, demonstrating no exposure margins to the recommended maximum clinical dose.

In one study, ALT plasma levels were increased by up to 4-fold following administration of 1.5 mg/kg/day to obese dogs. Abnormalities in erythrocyte morphology (Burr cells) were observed at 2.5 mg/kg in dogs. This finding is uncommon in dogs and may represent an abnormality in cell membrane lipid structure, secondary to low cholesterol levels in treated animals. Erythrocyte parameters, in general, were not impacted by the finding of Burr cells. In the 3-month oral toxicity study, slight to moderate numbers of Burr cells were observed for all animals in the mid and high dose groups on Day 28, 56, and/or 84 of the study. The presence of Burr cells did not result in major changes in red cell parameters. A slight decrease in haemoglobin concentration and haematocrit for males was observed at Day 84 in the high dose group. The haematology results for dogs in the 14-day and 3-month oral toxicity studies in dogs indicate that the finding of Burr cells had little impact on erythrocyte parameters.

The effect of dirlotapide treatment on steroid hormone synthesis showed that although Slentrol has a moderate effect on levels of circulatory cholesterol, the magnitude of this effect is not sufficient for it to be likely that significant effects on steroid hormone synthesis would occur. In long-term (up to 12 months) safety and efficacy studies there is no physiological evidence of steroid hormone dysfunction as a consequence of Slentrol therapy. In addition, the observation was only made at doses in excess of those indicated for Slentrol.

Reproductive toxicity, including teratogenicity

No studies were performed on female or male fertility or reproductive performance. The safety in breeding animals has not been demonstrated. As a consequence, a warning regarding use in breeding animals is given in the SPC section 4.5.

Embryotoxicity/foetotoxicity, including teratogenicity

Definitive and dose range-finding oral embryo-foetal development studies were conducted in rats and rabbits using dirlotapide in a SEDDS vehicle. Salivation was observed at 200 mg/kg, vaginal discharge in 1 dam at 200 mg/kg, mean food consumption and maternal corrected body weight were reduced at 50 and 200 mg/kg. Substantial increases in postimplantation loss, including early and late resorptions and a reduction in the number of viable foetuses were observed at 50 and 200 mg/kg. A reduction in mean foetal body weight was observed at all dose levels and external anomalies (including midline closure defects, various tail defects and anal atresia) were noted in 67, 21, and 4 % of foetuses per litter in the 200, 50, and 10 mg/kg groups.

In a study in rabbits, foetal body weights were reduced at doses ≥ 100 mg/kg and foetal gross external findings were noted at 100 mg/kg/day with one foetus in each group noted with short tail and omphalocele. Dirlotapide showed reproductive toxicity in the rat and the rabbit at systemic exposure levels with no margins to clinical exposure. Embryolethality was observed in the rat at doses ≥ 50 mg/kg/day. Teratogenicity was observed in the rat at doses ≥ 10 mg/kg/day and developmental toxicity (reduced foetal body weight) was observed in the rat at doses ≥ 3 mg/kg/day and in the rabbit at doses ≥ 75 mg/kg/day. NOAELs for maternal toxicity and for developmental toxicity in the rat were 10 mg/kg/day and 1 mg/kg/day respectively, demonstrating no margins to the maximum recommended clinical dose. The NOAEL for maternal and developmental toxicity in the rabbit was 5 mg/kg/day, respectively, also without margins to the maximum recommended clinical dose.

During gestation, robust MTP mRNA expression and activity have been identified in the murine "inverted" yolk sac which encapsulates the embryo/foetus. Without this activity, lipophilic nutrients cannot be transferred to the embryo and the embryos die. Rats and rabbits, but not humans, share a similar yolk sac structure and function suggesting that the embryolethality observed following exposure to dirlotapide might not be relevant for humans. However, other mechanisms, relevant for the dog and human, causing embryolethality and teratogenicity cannot be excluded. Consequently, dirlotapide should not be used in pregnant bitches. This is reflected in the SPC where the use in pregnant and lactating bitches is not recommended. Given there are no clinical data to support use of the product during pregnancy and lactation, these conditions are contraindicated for treatment. The safety in breeding animals has not been demonstrated. In addition, a sentence stating "Laboratory studies in rats and rabbits have shown evidence of embryolethality, teratogenicity, and developmental toxicity" is added to section 4.7. "Do not use in pregnant or lactating bitches" was added in section 4.3 of the SPC. In addition, the risk for a pregnant woman accidentally ingesting dirlotapide is reflected in the SPC.

Mutagenicity

The mutagenicity and clastogenicity of dirlotapide have been evaluated in a battery of *in vitro* and *in vivo* studies. Dirlotapide was tested negative for genotoxicity in a bacterial gene mutation assay, chromosomal aberration assay in cultured human peripheral blood lymphocytes and the micronucleus test in rat bone marrow.

Dirlotapide tested negative for genotoxicity in the micronucleus test in rat bone marrow. A rat micronucleus test was performed at systemic exposure levels well in excess of the systemic exposure in dogs at the recommended therapeutic dose. Dirlotapide did not induce micronuclei formation in bone marrow of female or male rats at the maximum feasible IV dose of 10 mg/kg and it can be concluded that dirlotapide is not genotoxic.

Carcinogenicity

No carcinogenicity study was performed with dirlotapide. The battery of *in vitro* and *in vivo* genotoxicity tests shows that dirlotapide is not genotoxic.

Studies of other effects

The dermal irritation potential, the eye irritation potential and the potential to produce delayed-type hypersensitivity was evaluated for the active substance dirlotapide in accordance with GLP, OECD guidelines and the Commission Directive 92/69/EEC methods. Dirlotapide was not a dermal toxicant, dermal irritant or corrosive, or a dermal sensitiser, but was a minimal ocular irritant. Dirlotapide is a minimal ocular irritant. This is reflected in the SPC section 4.5 by the following statements "Slentrol may cause eye-irritation. Avoid contact with the eyes. If accidental eye exposure occurs, flush the eyes immediately with clean water."

Observations in humans

Dirlotapide has been administered orally in single dose studies to humans.

A cat study was conducted to evaluate the safety of 56 days of weight loss mediated by either administration of dirlotapide or by food restriction in obese cats. The study showed that the use of dirlotapide to induce weight loss in cats increased the risk of them developing histopathological and clinical signs of hepatic lipidosis, compared to weight loss induced through dietary restriction alone. Two out of 13 cats treated with dirlotapide developed an anorectic syndrome due to hepatic lipidosis and were euthanased. Cats differ from other monogastric species such as dogs and humans in the way in which they process fat in the liver. In consequence, hepatic lipidosis is one of the most common hepatobiliary disorders in cats and, unlike in other species, it is associated with a very high mortality rate. Hepatic lipidosis is an acquired disorder caused by the excessive accumulation of triglycerides in the cells of the liver, which ultimately interferes with the liver's ability to function. In the light of the findings, the CVMP agreed to contra-indicate the use of Slentrol in cats due to the risk of hepatic lipidosis.

Microbiological studies (studies on human gut flora and organisms used in food processing)

No microbiological studies were conducted. This is accepted since dirlotapide is indicated for use in dogs only (non food-producing species).

Studies on metabolites, impurities, other substances and formulation

There were no studies conducted on metabolites. The acute oral toxicity of the SEDDS vehicle used in the nonclinical toxicity studies was investigated in dogs. Oral administration of the SEDDS vehicle to dogs for 3 consecutive days was well tolerated at a dose volume of 0.25 ml. The majority of oral toxicity studies were performed using dirlotapide in the SEDDS vehicle and not the commercial formulation as preferred. However, pharmacokinetics following oral exposure of dirlotapide in the SEDDS vehicle was evaluated in dogs and substantial systemic exposure was demonstrated. It was concluded that the exposure in the non-clinical oral toxicity studies in rats and dogs using the SEDDS formulation is considered to be similar to or greater than that observed with MCT and that NOAEL values used from these studies are considered robust for supporting user safety.

User Safety

A satisfactory User Safety Assessment in accordance with the Guideline on User Safety (EMEA/CVMP/543/03-Final) comprising of an exposure assessment, hazard identification and risk characterisations for identified exposure scenarios was conducted. Dirlotapide is provided as a solution formulated in a medium-chain triglyceride (MCT) vehicle. The compound will be provided in a sealed vial, with an adaptor to accommodate an oral syringe, and will be administered to the dog by the pet-owner directly in-the-mouth or by placing on food. Exposure scenarios identified as relevant

were: transcutaneous absorption following a spill, accidental ingestion by a 60 kg adult or child up to 15 kg and by a pregnant woman as well as exposure from cleaning and disposal of used syringes/pipettes. Appropriate risk management strategies are in place to address these risks.

Occupational safety studies demonstrate that dirlotapide does not present a risk in terms of dermal toxicity, dermal and ocular irritation and dermal sensitisation. Available information on the vehicle (MCT) for the final dirlotapide formulation indicates that it is classified as safe. Information provided indicates that the vehicle is non-toxic orally, not a dermal irritant, nonirritating to healthy and eczematous skin, not an ocular irritant and not a contact allergen.

Given the low inherent toxicity in mature species of dirlotapide and non-active excipient and the very low potential for systemic availability in humans following dermal exposure, there is a high level of confidence that the product is safe for use as directed and that the label instructions are appropriate to manage all conceivable risks to the pet owner due to accidental contact with the skin. The CVMP agreed that the construction of the bottle and syringe will minimise the risk for oral or dermal exposure by a toddler. The SPC includes appropriate statements to address these risks in section 4.5.

Environmental Risk Assessment

An Environmental Impact Assessment in accordance with the Guideline on Environmental Impact assessment for Veterinary Medicinal Products - Phase I, VICH Topic GL6 (CVMP/VICH/592/98-Final) was conducted. A Phase I assessment is accepted for this product as it is indicated for use in companion animals only.

Conclusion on safety

Several studies concerning the safety pharmacology of dirlotapide were conducted. Dirlotapide produced no neurofunctional effects and did not affect pulmonary or renal function in rats up to a dose of 50 mg/kg. However, due to the low bioavailability of dirlotapide, the systemic exposure obtained in the rats was below what is observed in dogs administered the highest recommended clinical dose (1 mg/kg/day). It is concluded that CNS, CV, pulmonary, or renal safety pharmacology issues are unlikely following therapeutic use of dirlotapide.

No oral single-dose toxicity studies were performed. However, given the overall low toxicity of dirlotapide, almost exclusively related to the pharmacological action and secondary effects from prolonged fasting, the lack of specific single-dose toxicity studies is acceptable.

The acute dermal toxicity of dirlotapide was sufficiently evaluated in the rat as a limit-test. No mortality, signs of systemic toxicity, signs of dermal irritation, bodyweight changes, or gross abnormalities at necropsy were noted at 2000 mg/kg.

A number of GLP and non-GLP repeat-dose toxicity studies were conducted in rats and dogs. In rats, the achieved systemic exposure at the highest dose of 50 mg/kg/day was lower than the exposure observed in a single-dose PK study in dogs administered dirlotapide at the maximum recommended clinical dose of 1 mg/kg. In dogs, toxicity was manifested as increases in serum AST and ALT at doses $\geq$ 1.5 mg/kg/day. This correlated with minimal hepatic single-cell necrosis at doses $\geq$ 10 mg/kg/day in the dose-range finding study only. Other findings were bodyweight loss, decreased serum lipids, decreased serum vitamin A and E, lipid accumulation in enterocytes, hepatic lipid accumulation, increased liver weights and associated inflammatory responses as well as secondary effects similar to effects expected from prolonged fasting. The NOAELs derived from the 3-month rat study and the 3-month dog study were 1 mg/kg/day and 0.25 mg/kg/day, demonstrating no exposure margins to the recommended maximum clinical dose.

Dirlotapide showed reproductive toxicity in the rat and the rabbit at systemic exposure levels with no margins to clinical exposure. Dirlotapide should not be used in pregnant bitches. This is reflected in the SPC where the use in pregnant and lactating bitches is not recommended. Given there are no clinical data to support use of the product during pregnancy and lactation, these conditions are

contraindicated for treatment. The safety in breeding animals has not been demonstrated and a suitable warning is included in the SPC.

During gestation, robust MTP mRNA expression and activity have been identified in the murine "inverted" yolk sac which encapsulates the embryo/foetus. Without this activity lipophilic nutrients cannot be transferred to the embryo and the embryos die. Rats and rabbits, but not humans, share a similar yolk sac structure and function suggesting that the embryolethality observed following exposure to dirlotapide might not be relevant for humans. However, other mechanisms, relevant for the dog and human, causing embryolethality and teratogenicity cannot be excluded. This is reflected in the SPC where the use in pregnant and lactating bitches is not recommended.

Dirlotapide tested negative for genotoxicity in a bacterial gene mutation assay, chromosomal aberration assay in cultured human peripheral blood lymphocytes, and the micronucleus test in rat bone marrow. An *in vivo* micronucleus test was conducted demonstrating bone marrow toxicity with sufficient margins to the recommended maximum clinical exposure. No carcinogenicity studies were performed with dirlotapide. This is acceptable as the lack of genotoxicity of the compound has been shown.

The dermal irritation potential, the eye irritation potential and the potential to produce delayed-type hypersensitivity was evaluated for the active substance dirlotapide in accordance with GLP, OECD guidelines and the Commission Directive 92/69/EEC methods. Dirlotapide is not a dermal irritant, or corrosive, or a dermal sensitiser, but was a minimal ocular irritant. This is reflected in section 4.5 of the SPC by the statements "If accidental eye exposure occurs, flush the eyes immediately with clean water." "Slentrol may cause eye-irritation. Avoid contact with the eyes."

The acute oral toxicity of the SEDDS vehicle used in the nonclinical toxicity studies was investigated in dogs. Oral administration of the SEDDS vehicle to dogs for 3 consecutive days was well tolerated at a dose volume of 0.25 ml. The majority of oral toxicity studies were performed using dirlotapide in the SEDDS vehicle and not the commercial formulation as preferred.

A satisfactory User Safety Assessment was conducted. It is agreed that the risk from exposure is negligible due to the low dermal absorption and low toxicity of dirlotapide and excipient.

An Environmental Impact Assessement in accordance with the Guideline on Environmental Impact assessment for Veterinary Medicinal Products - Phase I, VICH Topic GL6 (CVMP/VICH/592/98-Final) was conducted. The limited use and limited environmental exposure of this product will have limited environmental effects.

4. EFFICACY ASSESSMENT

Dirlotapide is a microsomal triglyceride transfer protein (MTP) inhibitor, a protein involved in the assembly and secretion of triglyceride-rich lipoproteins from enterocytes and hepatocytes. The compound selectively inhibits intestinal MTP thus acting in the enterocytes reducing intestinal fat absorption and indirectly suppressing appetite.

Pharmacodynamics

The ability of dirlotapide to inhibit intestinal MTP compared to liver MTP *in vivo* was determined using two mouse model studies. Inhibition of intestinal MTP was examined by measuring the degree of inhibition of intestinal absorption of radiolabeled triglyceride, whilst inhibition of liver MTP was determined by measuring serum triglyceride in a fasted state. Dirlotapide was a potent inhibitor of intestinal MTP and intestinal fat absorption with a dose giving 25% maximal effect (ED25) of 0.16 mg/kg. In contrast, dirlotapide was a relatively poor inhibitor of hepatic MTP with an ED25 of 6 mg/kg for lowering of serum triglyceride. A standard battery of *in vitro* tests has been performed. *In vivo* studies in mice were also submitted.

A significant decrease in food intake and body weight gain was seen in rats given dirlotapide compared to placebo. Food intake of rats receiving a low fat diet was also decreased in response to dirlotapide administration compared to placebo. A decrease in leptin in response to the reduced feed intake induced by dirlotapide was noted. Decrease in food intake as induced by dirlotapide administration results in a decrease in fat deposition in adipose tissue resulting in a decrease in leptin secretion, which is then intended to stimulate food intake in order to keep body weight at a constant level. This explains why leptin levels decrease in response to the reduced feed intake.

In exploratory dog studies, there was a clear relationship between oral dose and effect on body weight and feed intake with doses from 0 to the highest tested (0.6 mg/kg). There seems to be a clear dose effect relationship. This indicates that the reduced food intake is due to a true pharmacological effect on appetite rather than nausea or lowered palatability.

A study to characterise the effect of dirlotapide on the appetite of dogs during (7 days) and after (14 days) administration was conducted. Appetite was evaluated by observing the response of the dogs towards a treat offered by an animal handler. The animals eat less during treatment and the reason for this is not known. The risk that the reduced appetite is due to nausea or related negative perceptions was discussed. The reduced appetite may be due to a satiety signal, likely to be the peptide YY, released by the enterocyte in response to lipid accumulation in it and acting centrally at the brain level. Peptide YY (PYY) is a gut hormone whose secretion from the enterocyte is stimulated as a result of lipid accumulation in the enterocytes following MTP inhibition. The clinical signs of nausea (including lethargy) were recorded in the clinical trials but were transient. The factors and the mechanism leading to an increased incidence of emesis and diarrhoea in dirlotapide-treated dogs have not been identified but it could be assumed to be linked to the increased fat content in the faeces. The incidence of vomiting and diarrhoea is highest during the first month of treatment and decreases continuously thereafter. Thus, changes induced by the introduction of the dirlotapide treatment seem to play a role in the occurrence of vomiting and diarrhoea. The text included in section 4.6 in the SPC addresses this issue satisfactorily.

A study was conducted to evaluate the digestion and absorption of protein and fat during dirlotapide treatment to investigate if dogs will achieve a balanced nutritional intake, even when food intake is reduced. There were no significant effects of diet or treatment on the apparent digestibility of protein. The results indicate that the digestibility of fat is lowered by about 10% during treatment. Thus, the absorption of essential fatty acids and fat soluble vitamins could be affected. The faecal contents of nutrients were investigated after administration of a high dose of dirlotapide (0.3 mg/kg) for 5 weeks and compared to placebo in obese dogs. The only significant difference found between groups was a rather minor difference of apparent fat digestibility as compared to baseline. Despite the direct mechanism of action of dirlotapide being the inhibition of fat absorption, this inhibition is only partial

and plays a minor contributing role in the weight loss observed following treatment with dirlotapide, with the major contribution to the weight loss being the decrease in food intake. Assuming a reduction in absorption of fat-soluble vitamins and essential fatty acids similar to the relatively slight decrease (by about 6%) observed in fat apparent digestibility, deficiencies in fat-soluble vitamins or essential fatty acids following long-term use of dirlotapide (up to one year) are unlikely. This was confirmed by the fact that tissue levels of Vitamin E were not depleted and were even slightly increased following one year or nine months of dirlotapide treatment in two long-term safety studies, respectively. Indeed, blood levels of fat-soluble vitamins were substantially reduced during dirlotapide treatment, but it has been shown that this was more the consequence of the decrease in blood lipoprotein and cholesterol levels as well as of their redistribution within the body (change in blood/tissue ratio) rather than a substantial depletion of their total stock within the body. Therefore, the need to supplement diets offered to dirlotapide treated animals with fat soluble vitamins and/or essential fatty acids is not deemed necessary. However, the veterinarian should check that nutritional requirements in fat-soluble vitamins and essential fatty acids are covered by the actual quantities of food consumed.

It was shown in a separate study that dirlotapide acts locally as no effect was found after intravenous administration. The weight loss efficacy of once daily oral administration of dirlotapide was evaluated in obese spayed and neutered beagle dogs at a dosage that is adjusted for each animal to achieve the target weight loss of 1 to 2% of body weight per week for 12 weeks, followed by a dosage that is adjusted to maintain body weight for 4 weeks. The initial dose was found to be unnecessarily high as a lower dose was sufficient for achieving the target weight reduction.

Several studies investigated the pharmacodynamics of dirlotapide. The cellular target was found to be inhibition of the microsomal triglyceride transfer protein (MTP) with high selectivity. The effect is mediated locally as dirlotapide was not efficacious after intravenous administration. Due to the inhibition of MTP in the enterocytes the absorption of triglycerides from the intestine is reduced. This is recorded as increased amounts of triglycerides in the faeces. In addition, the food intake is reduced. The factors and the mechanism leading to an increased incidence of emesis and diarrhoea in dirlotapide-treated dogs have not been identified, however, adequate warnings are included in the SPC section 4.6 to address the incidence seen in studies.

Tolerance in the target species

The tolerance of dirlotapide in the target species was studied in an exploratory 14-day oral toxicity study in beagle dogs and an exploratory 3-month oral safety study in obese beagle dogs.

No mortality was observed. Sporadic occurrence of emesis and loose stools were observed in all groups, including the controls. Reduced mean body weight, body weight gain, and food consumption was observed in all dirlotapide dose groups. Clinical pathology and histopathology findings were generally consistent with the pharmacological effect of a MTP inhibitor on the intestinal tract and liver and the subsequent decrease in nutritional status and ensuing catabolic state associated with weight loss. Dose-related reduced serum cholesterol, high density lipoproteins were observed. Non-dose related decreases in various haematology parameters (reticulocyte counts) and serum chemistry parameters (total protein, albumin, calcium, glucose, and blood urea nitrogen) were noted generally across all dirlotapide dose groups. Additionally there were non-dose-related increases in serum ALT and AST noted across all dirlotapide dose groups.

Necropsy findings were limited to non-dose-related decreases in organ weights (liver, kidney and heart). Microscopically the accumulation of lipid in enterocytes at the intestinal villi was noted across all dirlotapide dose groups. In the pancreas there was minimal to moderate non-dose-related depletion of zymogen in all treated groups in both sexes. Mild periportal hepatocyte lipid accumulation was only observed at doses of at least 2.5 mg/kg and without any evidence of degeneration or necrosis. Serum biochemistry results, including liver enzymes and cholesterol, for the study where periportal hepatocyte lipid accumulation was observed, shows that no dose or sex effect was observed in ALT or AST increases or ALP or GGT slight decreases. Cholesterol decreases were similar between sexes and followed a dose related pattern. No correlation was identified between ALT / AST increases, ALP / GGT decreases or cholesterol decrease and periportal fatty accumulation in the liver.

Recommendations are included in section 4.5 of the SPC on when to stop treatment due to possible liver effects.

Decreases were noted in absolute organ weights (i.e., liver, kidney, adrenals and heart) at all dirlotapide dose groups and were proportional to the reductions in body weight. Necropsy findings included the presence of unabsorbed dietary fat along the lumenal surface of the small intestine in all dirlotapide dose groups. Microscopically, the accumulation of lipid in enterocytes at the intestinal villi was noted across all dirlotapide dose groups and considered to be a direct consequence of impaired lipid transfer through the intestinal mucosa. Additionally, slight dilation of lacteals at the tips of the intestinal villi was noted and considered a secondary change related to modified fluid transport across the mucosal barrier. In the liver, glycogen was diminished across all dirlotapide dose groups, and hepatic Kupffer cell pigmentation (i.e., iron-containing pigments) was noted at 1.5 mg/kg and 2.5 mg/kg. There was no evidence of adverse histopathology (i.e., necrosis, degeneration or inflammation) in the liver or intestine. All findings observed in this study were considered to be reversible.

Based on safety data collected from the field studies, 0.5 mg/kg/day appears to be an acceptable daily dose since 1) there were no clinical signs of liver disease or reduced liver function, 2) the elevations in liver enzymes were at a more acceptable level and declined with time even if treatment with dirlotapide was continued, 3) the increases in liver enzymes were reversible on cessation of treatment. 4) 1 mg/kg was not administered in the field studies. The safety of doses > 0.5 mg/kg was justified. No signs of liver damage in the form of histo-pathological lesions associated with ALT elevations were detected in the target animal safety study at dosages up to 2.5 mg/kg. The ALT increases were reversible at all dosages (up to 2.5 mg/kg) on cessation of treatment. There is a clinical need to use dosages up to 1.0 mg/kg current body weight, because more than a quarter of the treated patients may require dosages greater than 0.5 mg/kg current body weight, beyond four months of treatment. The CVMP concluded that 1.0 mg/kg is not associated to an unacceptable risk increase as compared to 0.5mg/kg.

The safety of dirlotapide has been demonstrated robustly under both laboratory and field conditions when used in over 780 dogs of a variety of breeds and bodyweights. The experience gathered in the clinical progamme did not indicate any evidence of liver problems related to dirlotapide at doses up to 1.0 mg/kg. The CVMP included the following statements in the SPC:
• Do not use in animals with impaired liver function. – section 4.3
• Any clinical indication of liver disease or dysfunction during treatment should be investigated through the evaluation of liver function. Any indication of progressive liver damage or of dysfunction should result in the discontinuation of the treatment. - section 4.5
• The duration of treatment with the product must not exceed 12 months and the dose of the product must not exceed a maximum of 0.2 ml/kg current body weight (1 mg/kg dirlotapide). – section 4.9
In conclusion, the CVMP accepts that the measures in place are responsible and reflect the appropriate steps required to ensure that an animal is not placed at risk of liver damage or deficiency during treatment with dirlotapide.

CLINICAL STUDIES

Laboratory trials

A pivotal dose finding GCP study was conducted to evaluate the safety and efficacy of dirlotapide administered orally once daily for 28 days compared with a placebo in the treatment of excessive body weight in overweight neutered male and female adult Labradors and to characterise the dose-response relationship. At dosages of 0.1, 0.2 and 0.4 mg/kg dirlotapide, all dogs experienced a body weight loss, with a mean weekly weight loss of up to -1.76 % per week in the high dose group compared to +0.43 % in the placebo group. At dosages of 0.025 and 0.05 mg/kg, some dogs experienced either no weight loss or a weight gain. The overall change in feed intake over the 28 day treatment period when compared to the pre-treatment period ranged between –10.6% for 0.025 mg/kg and -44.0% for 0.4 mg/kg dirlotapide treated animals. The placebo group increased their mean feed intake over the study period with a mean percentage feed intake change of +11.5%. The weekly percentage changes in fat were between -0.33% (0.025 mg/kg) and –1.19% (0.4 mg/kg). The weekly fat mass loss was greater as the dosage increased. Adverse reactions recorded were diarrhoea and loose stools. This study shows a clear dose/effect relationship on group level although the variability is high. It is noted that all animals in the high dose group reduced their food intake with few cases of anorexia. The inappetence observed in several dogs during the pretreatment period can be explained by the changes of diet and feeding duration introduced at the start of acclimatisation and by the disruptions induced by the measurement procedures. On acclimatisation start, food was offered for only two hours during the day and it may have taken several days for some dogs to understand that they were allowed to consume food for only two hours each day.

A second GCP study was conducted to confirm the safety and efficacy of dirlotapide in the commercial formulation, compared with placebo, administered orally once daily for up to 52 weeks in the treatment of excessive body weight in dogs given diets of differing fat contents. The starting dose volume of 0.02 ml/kg for the placebo dogs was equivalent to 0.1 mg/kg dirlotapide which was the initial dose in the treated dogs. Three distinct phases were studied; the acclimatisation phase, the weight loss and retraining phase and the post treatment phase.

During the acclimatisation period, dogs had their details recorded, were physically examined, scored for body condition and weighed. The relevant quantity of food was offered once daily during the acclimatisation phase (from day –37) and throughout the weight loss and retraining phase. Food was offered for approximately two hours in the morning (after dosing where applicable) and any food remaining after this time was discarded.

The weight loss phase was up to 168 days. Day 0 was defined individually for each animal as the first day of treatment with placebo or dirlotapide. When a body conditioning score (BCS) of 5 was reached or on day 168 of the weight loss phase, the animal went into the retraining phase, or was removed from the study. The retraining phase had a duration of 84 days for some dogs, which was extended to duration of 196 days for the remaining dogs. From day 0 and throughout the weight loss and retraining phase, dogs were administered the placebo or dirlotapide once daily prior to the morning feed *per os.* During the weight loss phase, the dose volume was adjusted at each body weighing time point to maintain a weight loss between 1 – 3% per week as determined from the last dose adjustment. If body weight loss was < 1% per week since last adjustment, the dose volume was doubled. The rate of weight loss did not exceed 3% per week for any dog during the weight loss phase. During the retraining phase, the body weight was maintained to ±5% body weight at the end of the weight loss phase by adjusting the dose to effect. Towards the end of the retraining phase, all remaining dogs on study were examined by an ophthalmologist for specific clinical signs of vitamin deficiencies, i.e. corneal abnormalities, papillodema, retinal lesions and xeropthalmia and they were also examined by a veterinarian for specific clinical signs of vitamin deficiencies, including lameness and petechia.

The post-treatment phase for animals was for 28 to 31 days. No treatments were given. Body weights were measured and recorded prior to feeding on days 27 and 28 of the post treatment phase. Food was offered for approximately two hours in the morning and food remaining after this time was discarded.

Complete dry food with a fat content of approximately 5, 10 or 15% was offered to all dogs at 1.2 x maintenance energy requirements throughout the acclimatisation period, weight loss and retraining phase and at 90% of what was eaten during the last period of recording feed consumption at the end of the retraining phase for the post treatment phase. Despite this some animals immediately started to increase in weight during post treatment and weight gain was up to a similar weekly magnitude as was weight loss during the weight loss phase.

The CVMP concluded that treatment with Slentrol over a period of 52 weeks to dogs with excessive body weight on diets with different fat content was safe and efficacious, resulting in a loss of body weight, due to a loss in fat mass and not lean mass and a decrease in feed intake. This efficacy and safety trial had a starting dosing regimen starting at 0.1 mg/kg, instead of 0.05 mg/kg. A dose adjustment schedule different from the final one is applied during the retraining phase.

The results of the study demonstrate that there is cumulative weight reduction of about 20% during the weight loss phase (168 days). There is a trend towards proportionality between fat content in feed and weight reduction. This is also indicated by the inverse proportionality between adjusted dose and fat content. During the retraining phase (196 days) a continued weight reduction is seen in the treated groups; the cumulative weight reduction is around 5%. The placebo dogs immediately gained weight again, between 7 and 25% proportionally depending on fat content in feed. For dirlotapide treated animals during the weight loss phase (WL), feed intake decreased by 17 %, whereas feed intake increased by 10 % during the retraining phase (RT), likely to be due to a concurrent reduction in treatment dose. Surprisingly weight reduction continued during RT despite dose reduction and increased food intake.

CVMP agreed that there are clear trends to indicate that dirlotapide treatment is connected to increased ALT, AST and decreased Albumin, ALP, Ca, Cholesterol, Globulins, Total protein and K. As earlier pointed out, increased ALT and decreased Cholesterol are the most pronounced effects. Apart from a few individual ALT increases above the reference range limit for a few monthly time points, the above described pattern is not considered to be of concern. They are rather to be seen as expected events secondary to the pharmacologic action of dirlotapide.

An increased variability of triglyceride levels in individual animals was noted during treatment. The slight mean increase in S-triglyceride values is believed to result from the balance of two opposite mechanisms induced by dirlotapide throughout the treatment period, which are the reduction of intestinal absorption of triglycerides and the increase of their release from body fat stores (induced by the negative body energy balance), with a slight mean advantage of the latter effect over the former one. Circulating concentrations of triglycerides reflect the balance between triglyceride absorption by the small intestine, synthesis/secretion by the hepatocytes and uptake by the adipose tissue. The slightly increased but more variable levels of triglycerides in dirlotapide-treated animals are considered to be the result of those two opposite mechanisms and of the metabolic adaptations induced by dirlotapide throughout the treatment period.

It was seen that dirlotapide causes a lowering of plasma vitamin A and E- levels in this study. It appears as if adipose vitamin E levels are increased by treatment.

There appears to be a link between fat content in feed and weight reduction. The study has demonstrated that significant weight loss (greater than 0.5% per week) can be achieved irrespective of the fat content of the diet. However, the efficacy becomes significantly higher, as the fat content of the diet increases from 5% to 10% and 15%. When used with low fat diets, dirlotapide should be used at higher dose levels to get comparable efficacy levels to those achieved with normal or high fat diets. These adjustments of dose level will occur automatically by following the dosing regimen proposed in the package leaflet and SPC. The studies have demonstrated that dirlotapide can be combined with all types of commercial diets regarding fat content and provides significant and reliable weight loss in dogs, regardless of the diet offered to the dog. Weight loss rates tend to be slightly higher and required doses lower with high fat content diets. Consequently, there is no need to recommend any type of diet or feed composition to be used when on treatment, apart from the fact that essential nutritional

requirements (proteins, vitamins, essential fatty acids, minerals) should be covered by the actual food intake observed with dirlotapide. This is reflected in section 4.4 of the SPC.

Change in body weight after treatment cessation has been evaluated in two phases, using two different feeding approaches (overfeeding or restricted feeding) during this study. During the retraining phase, dogs receiving placebo were offered food in the same quantities as during the acclimatisation and the weight loss phases, that is at 1.2 times calculated maintenance energy requirement for the starting body weight (i.e. before weight loss). In all treatment groups dogs increased their food intake and regained weight, with the weight rebound being maximum during the first month following dirlotapide cessation. As animals were overfed, this weight rebound was expected. CVMP accepted that metabolism is altered during feed reduction to increase feed conversion rate and that this mechanism is not specifically connected to any effect of dirlotapide. This finding stresses the importance of considering this therapy solely as a potential aid in a feed management programme where correct feed adjustment is in any situation the most important tool for obtaining permanent success. This is reflected in the indication in section 4.2 of the SPC for the product.

Field trials

EU field studies - efficacy and safety studies

Efficacy and safety of Dirlotapide in the treatment of excessive body weight in dogs
This was a GCP study to evaluate safety and efficacy, during three successive phases of weight loss (up to 28 weeks) retraining (12 weeks) and post-treatment (4 weeks), of Slentrol administered orally once daily, compared with placebo in the treatment of excessive body weight in over 250 dogs. This was a multi centre, masked, placebo-controlled field trial with three different dosing regimens.

Dogs intended for breeding and pregnant/lactating bitches, dogs with acute, or not medically controlled disease, clinical evidence of hypothyroidism, Cushing's syndrome, confirmed or suspected diabetes or any disease not compatible with food intake reduction were excluded from the study. Daily administration was performed by the dog owner, placing the dose in the back of the mouth with a syringe, or onto a small food portion. The test animals were randomly allocated into a dirlotapide (TO2) and a placebo (TO1) group according to a 2:1 ratio. Due to a high incidence of undesirable effects in the TO2 group (I), two additional dose-regimens (II, III) were consecutively introduced.

A. Weight loss phase (from day 0 until BCS of 5 was reached, or day 196)
In all groups after day 28, individual dose adjustments were performed every 4th week, to obtain a continuous weight loss within pre-set limits: percent weekly weight loss from last dose adjustment should be more than 1% and less than 3 % of bodyweight. In addition, the dose was adjusted at irregular time intervals, in case of excessive weight loss or Suspected Adverse Drug Events (SADEs). The need for dose reduction due to excessive weight loss never occurred. In all phases, the maximum dose was 1mg/kg body weight. The starting dose was 0.2, 0.1 or 0.05 mg/kg with a doubling of that dose after 14 days in the last group and dose adjustment in all groups from day 28.

B. Retraining phase (84 days following phase A)
The goal was to maintain weight (± 5 % of weight at end of phase A). If at every 4th week visit the limits were found to be exceeded, the dose was either halved (> 5 % body weight loss) or doubled (> 5 % weight gain). In addition, the dose was adjusted at irregular basis.
Normal practice in the dog's home environment was applied. More than 75 % of daily food intake should be a nutritionally balanced commercial food; crude protein > 20% of dry matter. Daily ration level was maintained at the same level from start of the study until end of phase B. The amount of extra food (treats) were not controlled. During phase C, food ration was adjusted to maintain final body weight, based on food manufacturer's instructions and the actual quantities consumed during phase B.

At time of enrolment, the placebo treated dogs weighed on average 30.0 kg (range 20.0-103.0 kg) and the dirlotapide treated dogs weighed 28.6 kg (range 28.6-60.5 kg). Frequency of concomitant disease at time of enrolment was similar in the two groups and consisted mainly of locomotor disorders. Food

characteristics at time of enrolment were highly variable with no obvious differences between the two groups.

The percentage of animals withdrawn from the study for different reasons was presented. Most withdrawals occurred during the weight loss phase, during the first 84 days of the study. Mean number of days in the study was 114 days for the placebo group and 195 days for the dirlotapide treated group. Mean weight loss phase was longer in treatment regimen III (149 days), than in regimen II (135 days) and regimen I (102 days). Two animals were reported with SADE during the study, one hepatitis case in the placebo and a case of sudden death in dirlotapide group, dose regimen II. Necropsy was inconclusive in the latter case. Most animals (75 %) in to placebo group were removed for lack of efficacy, whereas in the dirlotapide group corresponding figures were 4.3 %, 14.9 % and 10.5 % for dose regime I, II and III respectively.

For all dose-groups taken together during the whole weight loss phase (C), weekly weight loss was significantly greater among dirlotapide-treated dogs compared to placebo-treated dogs, and no difference in total weight loss between treatment regimens I, II and III was noted. Individual variation was large in all dose groups. A similar difference regarding total weight change was evident when data were restricted to the first 84 days. However, at day 84 in dose group III, the difference in total weight loss was quite modest between the treatment group (10.4 %) and the placebo group (4.1 %). During the weight loss phase, body condition score improved in 57 %, 76 % and 82 % of dirlotapide treated dogs, in treatment I, II and II respectively, whereas improvement in the placebo group was minimal.

During the retraining phase, mean total weight loss was 2.3 % for the combined three treatment regimens and 0.2 % in the placebo groups. For the whole retraining period, in the combined three dirlotapide treatment groups, total weight change range for individual animals was between +18.4 % and -12.9 %.

During the 4 week post-treatment phase (C), mean total weight gain was 2.9 %, 2.7 % and 3.5 % in treatment regimen I, II and III respectively and variation was from +15.1 % to -13.8 %. In treatment regimen III, weekly weight gain during the post treatment phase was even higher (0.86 %), than was weight loss during the weight loss phase (0.76 %)

During the weight loss phase and the retraining phase, treatment dose varied considerably between animals (0.02 mg/kg-1 mg/kg). Non-compliance to dosing regime (percentage of days with incorrect dosing) was 21.8 %, 11.4 % and 7.8 % in dirlotapide treatment regimen I, II and III respectively, and varied between 2.4 % and 5.3 % in the three placebo groups.

The most common adverse reactions were of the digestive tract and these include gastritis, vomiting, diarrhoea and gastro-enteritis. Some behavioural, locomotor, skin and unknown effects were also recorded. Overall 63% of dirlotapide dogs and 35% of placebo treated dogs showed some adverse reactions during the study. The most commonly recorded clinical signs were related to the gastrointestinal tract, but lethargy was also a common sign. For all these signs, incidence was higher in the dirlotapide group. Thus, gastrointestinal signs and conditions should be considered adverse drug effects. The incidence of the most commonly occurring clinical signs was highest in dose regimen I and lowest in dose regimen III. For all dose regimens, few of these signs occurred during the retraining phase and only two cases of vomiting/diarrhoea was recorded during the post-treatment phase, in dose regimen II. Eighteen percent of dirlotapide animals vomited 3 times or more during the whole study period. The corresponding figure for placebo animals was 3 %. Diarrhoea was rare among placebo animals. Anorexia was a quite common event (12 %) during the first month of the weight loss phase.

The dose regimen starting with 0.05 mg/kg was as efficacious as the two higher dose regimens (initial dose 0.1 mg/kg or 0.2 mg/kg), resulting in a weight loss of 20.9 % after 28 weeks of weight loss therapy and a less than 5 % weight loss in only 10 % of treated animals after 84 days of treatment. The low dose was also better tolerated with a lower incidence of adverse drug events, which were mainly of gastro-intestinal origin. Health disturbances related to the gastrointestinal tract were most common, indicating a significant negative influence on animal wellbeing during the treatment period.

Gastrointestinal symptoms are obvious signs of discomfort. However, it was shown that treatment with dirlotapide is associated with a significant reduction in body weight after up to a 40 week long treatment phase. However, although the dog owners were instructed to feed the dogs to maintenance energy level after the end of the treatment phase, a substantial weight gain was noted during the 4 week long post treatment phase. Thus, the effect seems only temporary, if additional measures regarding exercise and feeding routines are not implemented. A reversible effect of the drug regarding fat absorption has been documented in other studies. The CVMP concluded that the ability to maintain body weight after the end of treatment is essential to support long-term benefit. The SPC in section 4.4 emphasises that an appropriate feeding regimen is essential for long term weight loss.

Efficacy and safety of dirlotapide in the treatment of excessive bodyweight in dogs

This GCP study was conducted to evaluate the efficacy and safety of Slentrol, compared with placebo, in the treatment of excessive weight in dogs in the EU. This was a multi centre, masked and randomised, placebo-controlled field trial with one dosing regimen in over 150 dogs. Dogs intended for breeding and pregnant/lactating bitches and dogs with acute, or not medically controlled disease, clinical evidence of hypothyroidism, Cushing's syndrome, confirmed or suspected diabetes or any disease not compatible with food intake reduction and dogs on medications not permitted during the study were excluded. Daily administration was performed by the owner, placing the dose in the back of the mouth with a syringe, or onto a small food portion. The test animals were randomly allocated into a dirlotapide (TO2) and a placebo (TO1) group. Three phases are defined in the protocol:

A. Weight loss phase (from day 0 until BCS of 5 was reached, or day 196).
Initial dose was 0.05mg/kg. The dose was doubled on day 14, and if the lowest acceptable weekly weight reduction during this phase (< 0.7 %) was not obtained it was doubled again on day 28. Thereafter the dose was increased if necessary every 28 days by only 50 %, at maximum 3 additional times. If weekly weight loss during this phase was ≥ 0.7 % the dose was maintained.

B. Retraining phase (84 days following phase A)
The dose was adjusted to maintain (± 3 %) of the body weight achieved at the end of the "weight loss phase". At start of the retraining phase, the dose was either reduced or increased by 50%, or maintained, depending on whether weight change since the previous visit were above 0.7% weekly weight loss, above 0.7% weekly weight gain or within the +/-0.7 % weekly weight change range. During phase B the dose was either reduced or increased by 50 % to maintain weight within the ± 3 % weight achieved at the end of the weight loss phase.

In all phases, maximum dose was 1 mg/kg body weight. In addition, at any time during the study, the dose could be decreased by 25 %, after or not a few days of treatment suspension, if the patient had been anorexic for more than three consecutive days or in case of suspected adverse drug events intolerable to the owner or investigator.

Normal feeding practice in the dog's home environment was applied. More than 75 % of daily intake should be a nutritionally balanced commercial food; crude protein > 20% of dry matter. Daily ration level was maintained at the same level from start of the study until end of phase B. The amount of extra food (treats) was not controlled. During phase C, food ration was adjusted to maintain final body weight, based on food manufacturer's instructions and the actual quantities consumed during phase B.

Population characteristics regarding age, sex, breed, body weight and body condition score (BCS), were similar in the two treatment groups. At time of enrolment, concomitant disease was more common in the dirlotapide group (36.4 %), than in the placebo group (26.9 %). The most common conditions in both groups were from the musculoskeletal category, with 7.7 % and 13.1 % of the patient suffering from arthrosis (osteoarthritis) in T01 (placebo) and T02 respectively.

Withdrawal due to suspected adverse drug events (SADE) was more common in the dirlotapide group, whereas lack of efficacy was most common in the placebo group. All but one withdrawal occurred during the weight loss phase. At day 112, 80.0 % of the placebo animals and 8.4 % of the dirlotapide animals were withdrawn due to lack of efficacy. Thirteen per cent were withdrawn due to SADEs

(including vomiting, lethargy, anorexia/inappetence, diarrhoea) and 11% due to lack of efficacy in the dirlotapide group throughout the whole study phase.

In the dirlotapide group 42.5 % of the animals entered the retraining phase at day 196, whereas the others entered at day 56-168 due to the fact their BCS had reached ≤ 5.

In the dirlotapide group at day 196, mean total weight loss was 18.4 % but variation was high. By day 112, weight loss in the dirlotapide and placebo group was 12.0 (±4.7)% and 1.6 (±4.2)%, respectively. Weekly weight loss over the whole weight loss phase was significantly higher in the dirlotapide group than in the placebo group.

During the retraining phase mean total weight loss was 1.5 % in the dirlotapide group but variation was large. During the corresponding period, placebo treated dogs lost on average 0.2 % body weight, however the number of animals was very small. During the post-treatment phase for dirlotapide animals, body weight gain was on average 2.7 %. In the dirlotapide group, weekly weight loss during the weight loss phases (0.70 %) was of a similar magnitude as weekly weight gain during the 4 week post-treatment phase (0.69 %).

Changes in BCS corresponded quite well with the changes in body weight recorded during the three different phases. During the weight loss phase, the treatment dose was increased continuously in the treatment group and between-animal variation was large at all time points. A similar large dose variation also occurred during the retraining phase.

The most commonly recorded clinical signs were related to the gastrointestinal tract. For digestive signs and systemic signs (apart from pyrexia), incidence was higher in the dirlotapide group. Thus, these signs and conditions, which occurred mainly during the weight loss phase, should be considered adverse drug effects. Apart from vomiting among 4.2 % of dirlotapide treated dogs, none of these effects occurred during the post-treatment phase.

For all signs considered as adverse drug events, monthly incidence was highest in the beginning of the study period. Vomiting, diarrhoea and lethargy occurred also in the placebo group, but the incidence was lower. For the whole study period, vomiting occurred for more than 3 days in 25 % and 1.9 % of the dirlotapide /placebo animals, respectively.

The treatment regimen applied in this study was efficacious, resulting in a mean weekly weight loss of 0.70 % during the weight loss phase and a mean weight loss of 18.4 % after 28 weeks of weight loss therapy. The treatment caused a significant reduction in body weight during the treatment period, although variation between individuals was large. Some weight reduction also occurred in the control group, suggesting some of the treatment effect was due to a non-controlled reduction in feed allowance. Immediately after treatment some animals started to gain weight of a similar weekly magnitude as weight was lost during the treatment phase, despite the fact feeding advice was given aimed at providing the dogs only maintenance energy requirements. Thus the benefit of medical treatment is considered temporary. The indication in section 4.2 of the SPC reflects this ‘as an aid in the treatment of overweight and obesity’ combined with appropriate dietary and exercise measures.

Three animals in the treatment group died of causes not likely associated to treatment and no other serious drug events were observed. However, in accordance with the first field study, the incidence of adverse drug events was quite high and consisted mainly of gastro-intestinal signs, lethargy and inappetence/anorexia. The treatment is considered safe, although some dogs experienced undesirable effects such as vomiting, diarrhoea, lethargy, anorexia and inappetence. Appropriate warning statements are included in section 4.6 of the SPC. Nevertheless, beneficial effects of treatment, regarding wellbeing, vitality and occurrence of diseases which are associated with overweight were not measured.

Lameness was reported in EU field studies at incidences of 6.4%, 4.7%, 2.0% and 17.1% of dirlotapide treated dogs, compared to 1.2%, 0%, 2.0% and 10.2%, respectively, in placebo-treated dogs. The higher frequency of lameness observed in dirlotapide treated dogs was explained by the

study design (placebo animals remained on study for a shorter period of time) and by random variation. The EU field studies do not show any evidence, pattern or trend that would suggest that dirlotapide increases the incidence of lameness or of any specific condition associated with lameness (e.g. ligament injury, osteoarthritis, etc). However, it was noted that the study was neither designed nor statistically powered to provide any support for a positive effect of treatment on a parameter generally claimed to benefit from weight reduction.

The risk for rapid reduction in body weight and loss of essential nutrients if a reduced energy diet is introduced during treatment was discussed. It was accepted that there is no risk for rapid body weight loss if a reduced energy diet is introduced during treatment because the dose of dirlotapide is adjusted according to effect to achieve a body weight loss greater than 0.7% and lower than 3% per week. In addition, the loss of essential nutrients is unlikely given that they are incorporated in greater concentrations in commercial reduced energy diets. No signs of fat soluble vitamin deficiency were seen in the studies. According to the results from one field study, dose adjustment due to excessive weight loss never occurred, suggesting this is an unlikely event.

A summary of the observed drug incompatibilities seen across all clinical studies was provided. No incompatibilities were seen and all main therapeutic classes were represented, including anti-inflammatory drugs (including NSAIDs), antimicrobials, parasiticides, vaccines, dietary supplements, vitamins, hormones and cardiovascular drugs. It was difficult to draw any firm conclusions from efficacy studies not specifically evaluating interactions. The wording in the SPC section 4.8 reflects this.

The rationale for medical treatment of overweight in dogs would be to achieve positive effects on health and longevity. This would require not only appropriate weight reduction but also maintenance of body weight in the long term. Such effects are regarded as essential proof of a long-term benefit of treatment. The purpose of the post-treatment phase was to check whether the dirlotapide treatment would increase the frequency and magnitude of rebound compared to what is reported from conventional weight loss programmes or whether it would induce a systematic rebound even when the owner followed the feeding and exercise instructions properly. The two EU field studies have shown that 22% did not rebound at all during the 4-week period following dirlotapide discontinuation and 32% regained a minimal amount of weight (between 0 and 3%) during the same period. This demonstrated that the weight achieved at the end of the dirlotapide treatment period can be maintained, providing animals are fed and exercised according to the prescribed instructions. It is stated in section 4.4 of the SPC that treatment should be combined with lifestyle changes aiming at maintaining weight after treatment. According to the EU field studies it may be required the dogs are treated for 4-6 months before they reach target weight, a time period which CVMP believes would be long enough for any owner to adjust to a new feeding and training programme. CVMP therefore agreed that the posology should include only a weight loss phase. According to the suggested posology dirlotapide treatment would result in a slow and well controlled weight loss which is relevant for reducing the risk of weight rebound. The fact that a rapid rebound in appetite and body weight was not reported for dogs that rapidly terminated treatment due to withdrawal in the EU field studies confirms that a maintenance treatment period is not needed. Information that supports the safe continuous use of the product for up to 12 months has been provided.

Efficacy and safety of Dirlotapide administered once daily to obese dogs

The efficacy and safety of dirlotapide was studied at different initial doses that were adjusted individually to produce weight loss, followed by weight stabilisation when administered orally once daily, to obese dogs in the US. This was a multi centre, randomised, placebo-controlled field trial with three different dosing regimens. Dogs intended for breeding and pregnant/lactating bitches, or with clinical evidence of hypothyroidism, Cushing's syndrome, confirmed or suspected diabetes or any disease not compatible with food intake reduction were not included in the study. Nutritionally complete commercial canned and/or dry diet was given to the dogs in the same rations as before the study started. Treats and snacks were replaced with nutritionally balanced substitutes. More than 40 different breeds were represented in the study and the most common breeds were retrievers (34 %). At

time of enrolment, the most common concomitant medications were prophylaxis for endo/ectoparaticides, NSAIDs and antimicrobials for otic and topical use.

Three dosing regimens were consecutively tested.

A. Weight loss phase (Day 0-111). Initial dose: 0.3 mg/kg (regimen I), 0.1 mg/kg (regimen II) or 0.05 mg/kg (regimen III). In dose regimen II the dose was raised to 0.2 mg/kg at day 7, and to 0.3 mg/kg at day 14. In dose regimen III, the dose was raised to 0.2 mg/kg at day 14. From day 28 in all groups, the dose was once a month individually adjusted (in 25 % or 50 % increase-steps) to obtain a 1-3% weekly weight loss during the weight loss phase.

B. Retraining phase (Day 112-196). In all treatment regimens, the dose was adjusted (in 25 % or 50 % increase/decrease-steps) to maintain body weight constant (± 5 %)

C. Post-treatment phase. (Day 197-252). No medication.

Dirlotapide administered once daily and adjusted monthly was safe and appeared to produce similar weight loss at all of the initial dosage regimens. The lowest dosage (initial dose 0.05 mg/kg) appeared to cause the fewest adverse events, primarily emesis and anorexia. A significant weight reduction was noted among treated dogs. Weight loss was however also noted in the placebo group, especially for the highly selected population remaining in the study after day 112. This indicates that weight reduction was partly due to a reduced feed allowance during the study. Some improvement regarding activity is reported. At the end of the weight loss phase, an increased owner assessed, activity level was noted among 53 % of all dirlotapide treated dogs, and among only 19 % of the placebo dogs. No mortalities or serious adverse events attributed to treatment were noted.

No serious adverse drug related events were noted, but gastrointestinal signs were common which is considered a disadvantage for drug use. In addition, a marked increase in hepatic enzymes was noted in one dog during the study. Although no clinical signs of hepatic dysfunction were concurrently noted and the values were normalised after end of treatment, dogs with signs of hepatic dysfunction should not be treated. Vomiting, depression/lethargy, anorexia and diarrhoea were common clinical signs among dirlotapide treated animals. Anorexia, diarrhoea and lethargy/depression were more common in treatment regimen II than III, whereas vomiting incidence was equally common in the two dirlotapide treated groups. All those signs occurred mainly during the weight loss phase.

The incidence of lameness, which was registered in the range of 18% and 10.2% in treated and placebo compared to the EU studies at a level of approx. 2 and 1% respectively, was explained due to study design and by random variation. In this US study, only very few animals were included in the highest dose level group. The initial dosage regimen (0.3 mg/kg) was amended due to reports of vomiting coming from the clinical study that was ongoing in Europe. The dosage changes were applied in order to try to reduce the incidence of vomiting and resulted in the dose escalation regimen that is now recommended. It is acknowledged, taking into consideration the high frequency of adverse events and withdrawals in the 0.2mg/kg dosing regimen group reported in this study that the high initial dosing regimen (0.3mg/kg) would also be connected to a high frequency of adverse events.

Field effectiveness and safety of dirlotapide administered once daily to obese dogs

The study was conducted to evaluate the efficacy and safety of dirlotapide to produce weight loss when administered orally once daily to obese dogs in the US and Canada. This was a multi centre, masked, placebo-controlled field trial with over 250 dogs. The same inclusion criteria were applied as for the previous study. The test animals were randomly allocated into a dirlotapide or a placebo group. The dogs were treated for 112 days. The initial dose was 0.05 mg/kg, increased to 0.1 mg/kg at day 14 and from day 28 adjusted once a month to maintain a weekly weight loss $\geq$ 0.7 %. If the set target was not reached the dose was increased by 100 % the first time, then by 50 %. If the target was exceeded the dose was maintained at the same level. Nutritionally complete commercial canned and/or dry diet was given.

Dogs of different breeds (retrievers 26 %) aged 2-14 years were given placebo and dogs aged 1-13 years dirlotapide. Concomitant medication included: vaccines (15 % of all medications used), moxidectin (8.3 %), ivermectin/pyrantel (5.4 %), lufenuron/milbemycin (4.6 %), caprofen (4.2 %), fipronil (4 %), betamethazone/clotrimazole/gentamicin (3.1 %). The most commonly occurring protocol deviations concerned daily dose administration (40 %), incorrect dose or dose increase (20 %) and study visit window deviations (16 %). The dose was on average adjusted 3 times during the study period. No deaths occurred during the study. In the placebo group, withdrawals were mainly due to non-compliance with the protocol, whereas occurrence of adverse reactions were the most common withdrawal cause in treated dogs.

The most common clinical signs that occurred during the study period were of gastrointestinal origin. Regarding these signs, the difference between treated/untreated groups was of a minor magnitude. AST and ALT values were higher at the end of the study than at start, although in the dirlotapide group the values were always higher. ALP values seemed to decrease during dirlotapide treatment. Cholesterol values decreased in both treatment groups, whereas minor changes were noted regarding triglyceride values.

Dirlotapide treatment was associated with a significant weight reduction during the treatment period. In both groups, the most commonly occurring clinical adverse signs were of gastrointestinal origin. No difference between the two groups was noted. The fact that a severe suspected adverse drug event was noted associated to signs of hepatic dysfunction, emphasises that normal hepatic function should be verified by relevant diagnostic procedures before any dirlotapide treatment is initiated. No other obviously treatment-associated health disturbances were noted.

Conclusion on field studies

Two pivotal EU field studies, as well as the two US field safety studies were conducted, involving about 800 dogs. The dose regimen starting with 0.05 mg/kg was shown to be as efficacious as two higher dose regimens (initial dose 0.1 mg/kg or 0.2 mg/kg), resulting in a weight loss of 20.9 % after 28 weeks of weight loss therapy and a less than 5 % weight loss in only 10 % of treated animals after 84 days of treatment. The low dose was also better tolerated with a lower incidence of adverse drug events, which were mainly of gastro-intestinal origin. The starting dose selected is therefore 0.05mg/kg with the dose progression shown in section 4.9 of the SPC. The treatment regimen applied was efficacious, resulting in a mean weekly weight loss of 0.70 % during the weight loss phase and a mean weight loss of 18.4 % after 28 weeks of weight loss therapy. The treatment caused a significant reduction in body weight during the treatment period, although variation between individuals was large. Some weight reduction also occurred in the control group, suggesting some of the treatment effect was due to a non-controlled reduction in feed allowance. Immediately after treatment some animals started to gain weight of a similar weekly magnitude as weight was lost during the treatment phase, despite the fact feeding advice was given aimed at providing the dogs only maintenance energy requirements. Thus the benefit of medical treatment is considered temporary. To minimise rebound, a slow weight loss rate of about 1% per week is recommended, along with a gradual and constant monitoring of food intake according to maintenance needs during several months. The indication in section 4.2 of the SPC reflects this ‘as an aid in the treatment of overweight and obesity’ combined with appropriate dietary and exercise measures.

The most common adverse reactions in the field studies were of the digestive tract and these include gastritis, vomiting, diarrhoea and gastro-enteritis. Some behavioural, locomotor, skin and unknown effects were also recorded. Overall 63% of dirlotapide dogs and 35% of placebo treated dogs showed some adverse reactions during the study. The target animal safety studies confirm that hepatic enzymes may increase considerably at high dose level, but no sign of liver damage, apart from lipid accumulation, was observed. In the EU studies, about 10% of the animals receiving dirlotapide were withdrawn due to their owners’ intolerance of the clinical signs. The most common reactions were gastro-intestinal signs, lethargy and inappetence/anorexia. Appropriate warning statements are included in the SPC.

5. BENEFIT-RISK BALANCE

Slentrol contains the active substance dirlotapide and medium-chain triglyceride oil as the only excipient. Slentrol is presented as a 5 mg/ml oral solution for dogs in 20 ml, 50 ml and 150 ml white polypropylene (PP) bottles with a low density polyethylene bottle adapter. Two dosing devices are supplied with each bottle. The solution is manufactured using a standard manufacturing process involving simple dissolution of the active substance in the solvent. Process validation has been carried out on pilot scale batches and adequate in-process controls are detailed for the manufacturing process. The excipient has been fully characterised. Details of the manufacture of the active substance in a three step process from three starting materials are described in detail. The only impurity (the enantiomer) found above VICH qualification limits has been qualified in toxicological studies. The veterinary medicinal product specification include tests for active substance content and identity, chromatographic purity, water content and fill volume. Analytical methods and validation for the veterinary medicinal product are generally considered acceptable and in line with VICH GL 2. Batch data for several batches are in accordance with the specification. Impurities are controlled in line with VICH Topic GL10 - Impurities in New Veterinary Drug Substances.

The starting materials used in the production of the final product have all been declared in compliance with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Council Directive 2001/82/EC as amended.

Stability data under VICH conditions have demonstrated that changes in stereochemical purity do not occur on storage. A shelf-life of 2 years without storage restrictions, except that the product shall be stored in the original container, was approved. An in-use shelf-life of 3 months was agreed.

The safety studies submitted adequately characterised the acute toxicity of dirlotapide in repeat dose studies in both rats and dogs. No oral single dose toxicity studies were performed. However, the safety margin following acute oral exposure is very high. Significant changes occurring at the recommended dosage were primarily confined to alterations in serum parameters (phospholipids, cholesterol, triglycerides etc.) and vacuolation/lipid droplet formation in the intestines and liver. In dogs, toxicity was manifested as increases in serum AST and ALT at doses $\geq$ 1.5 mg/kg/day. This correlated with minimal hepatic single-cell necrosis at doses $\geq$ 10 mg/kg/day in the dose-range finding study only. Other findings were effects consistent with the pharmacological action of a microsomal triglyceride transfer protein (MTP) inhibitor (bodyweight loss, decreased serum lipids, decreased serum vitamin A and E, lipid accumulation in enterocytes, hepatic lipid accumulation, increased liver weights and associated inflammatory responses) as well as secondary effects similar to effects expected from prolonged fasting. The NOAELs derived from the 3-month rat study and the 3-month dog study were 1 mg/kg/day and 0.25 mg/kg/day, demonstrating no exposure margins to the recommended maximum clinical dose.

Vomiting was the most frequent side-effect, but anorexia/decreased appetite, lethargy or diarrhoea were also seen. Other side effects were related to sporadic and mild ALT elevations not associated with noticeable liver changes. Appropriate warnings are included in the SPC section 4.6.

No studies were performed on female or male fertility or reproductive performance. MTP inhibitors as a class, have the potential to disrupt yolk sac development and laboratory studies on rats and rabbits have shown evidence of embryolethality, teratogenicity, and developmental toxicity. There is therefore a contraindication for use in pregnant or lactating bitches and use in dogs intended for breeding should be subject to a risk-benefit analysis.

Dirlotapide tested negative for genotoxicity in the micronucleus test in rat bone marrow. Based on the absence of any known structural alerts, negative mutagenicity findings and the absence of any pre-neoplastic lesions in repeat-dose studies, no carcinogenicity studies were performed. Dirlotapide is not a dermal toxicant, dermal irritant or corrosive, or a dermal sensitiser, but was a minimal ocular irritant. This is reflected in the SPC with appropriate warnings in section 4.5.

A satisfactory user safety assessment was conducted. The CVMP concluded that the risk from exposure is negligible because of low dermal absorption and low toxicity both of dirlotapide and the excipient.

An environmental risk assessment stopped in Phase I. As the product is intended for use in individual companion animals, exposure of the environment is likely to be low and no further information is considered necessary.

The tolerance of dirlotapide in the dog was studied in an exploratory 14-day oral toxicity study in beagle dogs and an exploratory 3-month oral safety study in beagle dogs. No mortality was observed and all findings were considered to be reversible.

The health risks of obesity have been well documented, yet many dogs and owners have not been successful using traditional methods of weight loss, as shown by the increasing prevalence of obesity in pet populations. It is well recognised that dietary restriction associated with exercise and behavioural changes will achieve weight loss. Dietary restriction is traditionally based on voluntarily feeding reduced quantities of food and often results in failure due to the lack of owner compliance to the prescribed measures. Dirlotapide is not a replacement to these recommendations but an additional tool providing a reliable and consistent dietary calorie restriction.

The benefit of the dirlotapide treatment is that it does not depend on the compliance of the owner to dietary prescriptions and is efficacious with all types of diets, whether they are normal or specifically designed calorie restricted diets. The only difference with the conventional non-medical programmes using the dietary restriction approach is that dirlotapide reduces food intake and begging behaviour by controlling the dog's appetite. Weight loss rates tend to be slightly higher and required doses lower with high fat content diets. There is no need to recommend any type of diet or feed composition to be used when on treatment, apart from the fact that essential nutritional requirements (proteins, vitamins, essential fatty acids, minerals) should be covered by the actual food intake observed with dirlotapide. This is reflected in the SPC.

About 800 dogs in Europe and North America have been treated with dirlotapide in laboratory and clinical studies of various durations up to one year. No serious adverse reactions have been reported from any of the studies conducted using either the clinical dose or multiples of the clinical dose. The common adverse reactions from treatment at the recommended dose are vomiting, diarrhoea, inappetence, lethargy. In the EU studies, about 10% of the animals receiving dirlotapide were withdrawn due to their owners' intolerance of the clinical signs. However, these undesirable effects constitute a minor and manageable risk to animals.

The risk of weight rebound after dirlotapide treatment is discontinued is not specific to this product. To minimise rebound, a slow weight loss rate of about 1% per week is recommended, along with a gradual and constant monitoring of food intake according to maintenance needs during several months. Most changes in clinical biochemistry and haematology were consistent with the pharmacological action of MTP-inhibition and decreased food intake. Daily treatment with dirlotapide, showed sporadic, mild and generally transient ALT and AST elevations. Although damage to the liver due to dirlotapide has not been seen in studies at doses up to 2.5 mg/kg, the potential risk to the liver is minimised by following the recommendations in the SPC. The target animal safety studies confirm that hepatic enzymes may increase considerably at high dose level, but no sign of liver damage, apart from lipid accumulation, was observed.

Based on safety data collected from the field studies 0.5 mg/kg/day appears to be an acceptable daily dose. There is a clinical need to use dosages up to 1.0 mg/kg current body weight, beyond four months of treatment. The CVMP concluded that 1.0 mg/kg is not associated to an unacceptable risk increase as compared to 0.5 mg/kg.

Slentrol should be integrated in a weight management programme, to ensure benefits of weight loss are kept on the long term when the medical treatment is stopped. The continuation of treatment after target weight is obtained was not justified and thus treatment is only allowed until target weight is

obtained. CVMP accepts that when the product is used as recommended, the potential for significant adverse effects to treatment is low.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Slentrol were considered to be in accordance with the requirements of Council Directive 2004/28/EC, as amended.