SCIENTIFIC DISCUSSION

1 SUMMARY OF THE DOSSIER

Yarvitan, a 5 mg/ml, oral solution contains mitratapide as active substance. Mitratapide is a potent inhibitor of the microsomal triglyceride transfer protein (MTP). The benefits of Yarvitan are its ability to reduce bodyweight in adult dogs when given in accordance with the approved treatment schedule of 2 periods of 21 days with 14 days without treatment in between. The majority of overweight dogs are overweight from excess body fat. Several predisposing factors relate to the development of obesity in companion animals, including: advancing age, breed, neutering, excessive or inappropriate feeding and infrequent exercise or inactivity. The treatment with Yarvitan is given orally with food once daily. The most common side effects are vomiting, diarrhoea or softened stools.

2. QUALITY ASSESSMENT

Composition

Yarvitan oral solution contains 5 mg/ml mitratapide as active substance. Conventional pharmaceutical excipients (flavouring agent, anti-oxidant and solvent) are used and full details are included in the SPC.

Container

Yarvitan is presented in amber glass bottles with polypropylene child resistant caps with a low density polyethylene (LDPE) liner fitted with an insert for an LDPE/polystyrene dosing pipette. The dosing pipette is supplied separately to the bottle and two separate dosing pipettes sizes are available. A 4 ml pipette will be supplied with the 55 and 120 ml bottles and a 6 ml pipette with the 210 ml bottle.

Three container volumes are proposed: 55 ml (in 60 ml nominal bottle) - 120 ml (in 125 ml nominal bottle) - 210 ml (in 230 ml nominal bottle). All packaging components are suitable for pharmaceutical use. Pack sizes have been chosen with reference to the dosage regime and bodyweight of the target species (from 2 kg to 40 kg).

Typical certificates are provided for each of the components of the container. Food certification and/or compliance with Ph.Eur. requirements have been provided for all relevant plastic packaging components. Confirmation of compliance with applicable ISO standards for child resistant packaging was provided.

Clinical Trial Formula

Formulations used in early preclinical studies were modelled on an aqueous formulation in which a solubilising agent was used to aid dissolution of the active substance. These formulations were later replaced with the proposed formulation in which the solvent polyethylene glycol is used and no solubilising agent is necessary. Bioequivalence of these formulations with respect to postprandial triglyceride uptake in beagle dogs was investigated in a randomised study using a crossover design. Postprandial triglyceride uptake after administration of the 3 different formulations investigated was substantially lower than when no treatment was given and the reduction was comparable for all three formulations.

Preclinical and clinical studies were carried out using the final formulation.

Development Pharmaceutics

Early formulations were modelled on an aqueous formulation of the drug. In order to adapt this formulation for multidose veterinary use, investigations to establish suitable antimicrobial preservatives were carried out. Because of the relatively high solubility of mitratapide in polyethylene

glycol compared to other solvents commonly used in pharmaceutical products, this excipient was investigated as a potential solvent for the formulation. The solvent is also relatively well tolerated in dogs, is of low toxicity and is commonly used in pharmaceutical formulations. Polyethylene glycol does not sustain microbiological growth because of its low water content. The chosen formulation is self preserving and does not require an antimicrobial preservative.

Sucralose is included in the formulation as a sweetener. This excipient is permitted for use in food as per Directive 2004/46/EC.

During formulation development the inclusion of a radical scavenger was investigated with respect to reducing the formation of degradation products. Butylhydroxyanisole was selected as the preferred choice. Its concentration was then optimised in further studies which examined the extent of degradation in formulations containing butylhydroxyanisole.

Development studies were carried out in order to establish critical steps and to optimise the process. Parameters such as mixing time, temperature, mixing tools, particle size of the active substance and atmospheric conditions were investigated. Stress studies of the drug product demonstrate it to be susceptible to degradation due to acid, base, light and oxidative conditions. The amber glass bottle complies with Ph.Eur. requirements for light transmission and provides adequate protection from light.

Dose accuracy studies in line with Ph.Eur. 2.9.27 Uniformity of mass of delivered doses from multidose containers were presented for the 4 ml and 6 ml pipettes.

Method of manufacture

The manufacturing batch formula was presented for the proposed batch size. The manufacturing process, flow chart and in-process controls are described in detail in the dossier. The process is straightforward, involving sequential dissolution of the active substance and excipients in polyethylene glycol. In-process controls include completeness of dissolution, control of temperature throughout the process and fill volumes.

Satisfactory process validation data demonstrate the processes to be reliable and robust. A validation protocol for the commercial batches was presented.

Control of Starting Materials

Active Substance

Mitratapide ($C_{36}H_{41}C1N_8O_4S$) is not detailed in any pharmacopoeia and a detailed specification was provided including tests for appearance, identity, chromatographic purity, loss on drying, residue on ignition and assay. With the exception of two named impurities, limits for impurities are in line with VICH qualification and identification limits. The proposed limits for the two named impurities are in line with batch data and have been qualified by GLP toxicity studies.

Stereoisomeric purity is controlled by a stereoisomeric HPLC method. Polymorphism and particle size can potentially affect bioavailability. The active substance exists in three polymorphic forms, however, as the active is fully dissolved in the product formulation, polymorphism does not affect bioavailability. During validation of the manufacturing process of the product formulation, the effect of particle size on dissolution was investigated and the process was developed to be robust with respect to particle size of the active substance. Thus particle size does not affect bioavailability.

Structural characterisation of the active substance is provided (UV, IR, ^{1}H NMR, ^{13}C NMR and MS) along with a detailed physico-chemical characterisation.

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. Detailed specifications for all starting materials are provided. Satisfactory justification for each specification

limit for starting materials is provided. Satisfactory description of methods and methods validation are presented. The quality of both starting materials is supported by batch data from a number of pilot scale and full scale batches.

Class 3 solvents used in the process are controlled by the loss on drying limit of 0.5 %. Batch data for the class 2 solvent *N,N*-dimethylacetamide confirm that no concentrations higher than 10 % of the VICH limit were detected in the drug substance batches. Data provided for batches manufactured using the commercial process, was shown to be consistently within the specification limits. The residual solvents used in the manufacture of the starting materials are controlled to ensure that the absolute amounts of residual solvents, to which the animals are exposed, remain very low. The active substance specification is considered suitable to control the quality of the active substance.

Extensive discussion of potential impurities is included in the dossier. All potential impurities are controlled by process knowledge and the specifications for the two primary starting materials and the intermediate as well as the specification for the drug substance itself. Inclusion or exclusion of specific impurities on the specification is based on criticality analysis. There are two unspecified impurities, which are never detected above the VICH reporting threshold of 0.1 %w/w.

Stability batches were tested for appearance, loss on drying, assay, chromatographic purity, stereoisomeric purity and appearance. The methods used for assay and chromatographic purity have been validated with respect to their stability indicating nature (forced degradation study). No changes are observed in appearance, appearance of solution or water content. Specified impurities are detected in all batches tested. All remain within specification and do not fluctuate during the course of the study at any temperatures. The applicant provided the results of the stability study at 18 months for three batches at 25°C/60% RH and 30°C/65% RH. The results confirm, in line with guideline ICH Q1E, that a retest period of 30 months is justified.

Excipients

Conventional pharmaceutical excipients are used and they all comply with the relevant Ph.Eur. monograph for excipients listed in a pharmacopoeia. Typical certificates of analysis are presented for each excipient.

Confirmation was provided that sucralose is routinely tested to the full USP monograph specification. Certificates of Analysis for batches of Sucralose were provided. Sucralose has been accepted as a sweetener for inclusion on food in the EU by the amendment of Directive 94/35/EC in 2004. Confirmation of compliance with the requirements of Directive 95/31/EC for sucralose published in 2004 was provided.

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 Yarvitan 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 Yarvitan finished product including appearance, identity of the active, colour of solution, chromatographic purity, identification and assay of butylhydroxyanisole, deliverable volume, related substances and microbiological purity were provided. Skip testing of microbiological quality is acceptable given the non-aqueous nature of the formulation and the data presented to date. The absence of limits for stereoisomeric impurities on the release and shelf life specifications was justified.

Details of all test procedures and analytical methods (suitably validated) 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 applicant provided a large set of detailed data on various method upgrades throughout the analytical development of the finished drug product in order to provide substantial evidence of the increasing performance of the HPLC methods developed over time. 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

All batches are packed in amber glass bottles with an insert for the dosing pipette. The bottles are closed with a child resistant closure. All batches tested in the stability studies results remain within specification. Bracketing was applied with the smallest and largest pack sizes tested as these represent the extremes with respect to headspace volume. Testing consists of appearance, mitratapide assay, degradation products and butylhydroxyanisole assay. Microbiological quality (total viable aerobic count and pathogens) was also monitored. The specification applied throughout the shelf life is the same as that at release except that the limit for butylhydroxyanisole is amended. As the main solvent polyethylene glycol 400 is known to be very hygroscopic, information on the water content in the finished product following storage under accelerated conditions and in-use conditions was provided. Neither process conditions (manufacturing is performed in closed GMP state of the art vessels), nor the immediate packing material (glass bottle) raise major concerns on water absorption.

The product appears to be very stable on storage. No decrease in active substance content is observed and related substances all remain below the VICH reporting threshold of 0.3 %. It was demonstrated that no unacceptable change in stereochemical purity occurs during the proposed shelf life. Based on the presented data, a shelf life of three years was accepted for the oral solution.

In-use Stability Tests

An in-use study mimicking use of the product in practice, in line with EMEA/CVMP/127/95 has been performed. Samples were tested for appearance, mitratapide assay, degradation products and butylhydroxyanisole assay. Microbiological quality (total viable aerobic count and pathogens) was determined at the start and end of the test.

All results remain within specification. No decrease in active substance content is observed and related substances all remain below the VICH reporting threshold of 0.3 %. No change is seen in butylhydroxyanisole content. An in-use shelf-life of 3 months was accepted based on the data provided.

OVERALL CONCLUSION ON QUALITY

Yarvitan contains the active substance mitratapide and is presented as a non-aqueous 5 mg/ml oral solution. The product is packaged in type III glass bottles of 55 ml, 120 ml and 210 ml. A dosing pipette is supplied with each bottle. The formulation is well described and the container/closure systems are suitable.

The solution is manufactured using a standard manufacturing process involving simple dissolution of the excipients and active substance in the solvent. Process validation has been carried out on pilot scale batches and data for full scale batches will be provided post authorisation. Detailed information regarding the manufacture and quality control of the novel active substance is provided in the dossier.

The finished product is manufactured using conventional pharmaceutical equipment and standard processing techniques. There are no critical steps, which require in-process controls, so all the critical parameters are tested at the final product stage. Suitable control tests on the finished product are

conducted using validated methods where appropriate. Batch data show that the finished product is within the specifications set. The finished product specification includes tests for active substance content and identity, antioxidant content and identity, chromatographic purity, deliverable volume and microbiological quality. Analytical methods and validation for the finished product are generally considered acceptable as well as in line with VICH GL 2.

The shelf life specifications for the product are essentially the same as for release. Stability data under VICH conditions has been presented for batches of product packed in the packaging proposed for marketing. A shelf-life of 2 years for the finished product and an in-use shelf-life of 3 months was accepted based on the data provided. The quality data provided are satisfactory and adhere to current guidelines.

3. SAFETY ASSESSMENT

Introduction

Mitratapide is indicated for the treatment of overweight and obesity in dogs. The molecule works by inhibiting a key enzyme involved in the absorption of dietary lipids called microsomal triglyceride transfer protein (MTP). Mitratapide inhibits MTP function at the level of the enterocyte. Hence, lipid absorption into the portal circulation is reduced. Mitratapide also has a slight appetite decreasing effect that is claimed to be associated with its mode of action. Mitratapide does not exert any central effects.

Safety Testing

Pharmacokinetics

The pharmacokinetic features of mitratapide have been well characterised in a number of studies on the mouse, rabbit, rat, dog and man. Mitratapide is rapidly absorbed following oral administration, with maximum plasma concentrations occurring within 3-5 hours following a single oral dose. Prior to entering the systemic circulation, a proportion of the absorbed mitratapide undergoes first pass metabolism in the liver. Mitratapide is extensively metabolised to, primarily, two sulphoxide metabolites (M1 and M2) and a sulphone metabolite (M3); the three metabolites account for up to 90 % of total exposure within 24 hours. Peak concentrations of M1 and M2 are reached by 2 hours, with peak plasma concentrations of M3 being reached at 6-8 hours; after repeated oral dosing, M3 is the predominant substance in plasma and tissues. Based on the data presented in the pharmacodynamic section, it is noted that the metabolites, in particular M2 and M3, have been shown to possess significant pharmacological activity. Peak plasma concentrations of the three metabolites were reached twice as early after oral dosing as compared to intravenous dosing indicating that mitratapide is more rapidly metabolised after oral administration due to first pass metabolism.

In repeat dose studies in the rat, total exposure to the parent compound and to metabolites was 1.7 to 2.4 times higher in females compared to males, suggesting a more pronounced metabolism in males. An important pharmacokinetic observation in the target species is the inverse relation between the plasma concentrations of the parent substance and the reduction of the uptake of triglycerides after a meal. Optimal efficacy is obtained when Yarvitan is administered together with food. The dose finding and pharmacokinetic study was conducted in accordance with this dosing recommendation. To explore whether another relationship existed between the pharmacokinetics of mitratapide and its relevant metabolites and its overall effect on bodyweight reduction, a compilation was made of the data available. The bodyweight changes achieved in the individual dogs at the end of the 21-day treatment period and the steady state values of the Area Under the Curve (AUC) at the last dosing day were assembled for the 3 dose levels in the experiment for parent mitratapide, for the metabolites M1, M2 and M3 and also for the sum of parent mitratapide plus its metabolites. From the plots provided it can be deduced that for the low AUC values achieved with the dose of 0.31 mg/kg, there is no or only limited bodyweight decrease. At the higher doses, substantial bodyweight decreases are achieved with higher AUC values, but no evident correlation can be deduced. Based on the available pharmacokinetic parameters, a statistically justified PK/PD analysis is not feasible. Bioavailability following oral dosing was calculated to be 16.2-21.2 %.

Following absorption, parent compound and its metabolites are distributed to a wide range of tissues, with highest concentrations detected in the adrenals, liver and mucosa of the small intestine. Typically, concentrations of parent compound and metabolites in muscle, fat, brain and foetus were low. The data indicate that mitratapide has no central effect at the RTD. Mitratapide is eliminated from tissues, with the exception of the adrenals, at a rate similar to elimination from plasma. The plasma half-life of

parent compound when administered at a dose of 0.63 mg/kg is approximately 6 hours, with half-lives for the metabolites ranging from 9-12 hours for M1 and M2 and up to 45 hours for M3.

Based on a limited study with single oral dosing of radiolabelled drug in the rat, the primary excretion route is the faeces (up to 80-90 % of total dose). Based on preliminary data, it was observed that a higher plasma exposure was achieved for mitratapide and its metabolites in dogs that consumed little or no food in the hour prior to dosing when compared to dogs that consumed all of their feed. This relationship between feeding and bioavailability was investigated in a laboratory study. In that study, it was found that the test product was more efficacious when administered with food and that plasma concentrations of mitratapide and its metabolites tended to be lower when administered with food compared to when administered to fasted animals.

Toxicological studies

Single dose toxicity

A large number of single-dose toxicity studies were performed in laboratory animal species (mouse, rat, dog), though not all were in compliance with GLP. The studies submitted adequately characterised the acute toxicity of the compound at dose rates well in excess of the RTD in the dog (0.63 mg/kg BW). In some studies, rats were more sensitive to adverse effects of mitratapide than mice. Mortalities were only reported following IV administration in the rat. Thus, the safety margin following acute oral exposure is very high. Many of the adverse effects recorded in the dog were similar to those reported in repeat dose, tolerance and efficacy studies.

Repeated dose toxicity

A large number of studies that characterised the repeat dose toxicity profile of mitratapide in target and non-target species were presented. Some were GLP-compliant. Treatment periods ranged from 2 weeks to 3 months. The studies were noteworthy in terms of how reproducible the results were; this latter finding was largely independent of the study duration or dose rate. In general, mitratapide was well tolerated at the RTD. Significant changes occurring at this dosage level were primarily confined to alterations in serum parameters (phospholipids, cholesterol, triglycerides etc.) and vacuolation/lipid droplet deposition in the intestines and liver. At higher dose rates, mitratapide resulted in soft faeces and decreases in food intake and bodyweight gain. Total protein and albumin values were reduced in several studies and the mechanism involved remains unclear. Decreases in serum calcium values are likely to be related to hypoalbuminaemia. Although one study revealed no adverse effects on the renin-aldosterone system, potassium values were elevated in some reports submitted.

Alkaline phosphatase (AP) values in serum occasionally declined, again with no apparent explanation. A similar effect on alkaline phosphatase has been reported with other lipid lowering drugs. The CVMP accepted that the low AP values and reduced lipid absorption in treated animals have not been associated with any overt hepatic or systemic pathology. The CVMP also concluded that there is no indication that the reduced lipid absorption at the therapeutic dose of mitratapide has a relevant effect on hepatic function.

Species and sex differences were seen for the effect of mitratapide on adrenal function and in particular the effects on aldosterone and consequently serum electrolyte concentrations. More specifically, female rats were most sensitive to changes in aldosterone levels. Dosing mitratapide up to 5 mg/kg for three months did not result in a relevant effect on aldosterone concentrations in dogs. In the EU and US field trials, no statistically significant effect on serum potassium levels was observed in dogs treated with mitratapide compared to placebo. However, it should be noted that serum potassium values were elevated in a 2-month safety study in the dog using the RTD. Thus, the data are somewhat conflicting and not always reproducible. Biochemical data are included under section 4.6 of the SPC (Adverse Reactions), and a reference that hyperkalaemia was occasionally observed in some safety studies is included.

Reproductive toxicity, including teratogenicity

A single generation reproductive toxicity study showed no adverse effects of mitratapide treatment on a variety of reproductive parameters. Copulation rates, fertility rates, the numbers of foetuses and pre- and post-implantation losses were unaffected by treatment. Two GLP-compliant developmental toxicity studies were performed in the rat and rabbit. Although maternal toxicity and reduced reproductive performance was evident at high-dose rates, only minor variations and deviations were detected at dose levels well above the RTD in the dog. Mitratapide treatment was not associated with a significant increase in the incidence of serious malformations.

Mutagenicity

A reverse gene mutation test, bacterial reverse mutation test, mammalian forward gene mutation test and micronucleus test in mice were conducted in compliance with GLP. The battery of tests submitted is in agreement with VICH guidance. Precipitation was observed at relatively high concentrations. However, in agreement with the relevant OECD guideline, testing was performed up to (and in some cases beyond) the limit of solubility. Mitratapide did not exhibit any clear evidence of mutagenic potential in the battery of tests submitted. Mitratapide was considered negative under the conditions of the mouse lymphoma assay.

Carcinogenicity

No carcinogenicity studies were submitted in this application. 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 are considered necessary.

Microbiological studies (studies on human gut flora)

The potential for bacterial overgrowth following the use of mitratapide in the target species was adressed. The extensive package of preclinical and clinical safety and efficacy studies has not revealed any adverse effects that might suggest small intestinal bacterial overgrowth during mitratapide treatment in dogs. The CVMP concluded that treatment with mitratapide does not present a risk for bacterial overgrowth. This is evident from its mode of action and is confirmed by the data from the laboratory and clinical studies.

Studies on metabolites, impurities, other substances and formulation

Two impurities were detected at quite high concentrations, exceeding the VICH qualification threshold of 0.5 %. A toxicological qualification was provided for these two impurities. The batch of product evaluated in the Ames test had concentrations of one impurity below the VICH threshold. No additional Ames test has been conducted and justification for this was provided along with a statement signed by an independent Expert. It is noted that the concentrations of the impurity tested so far have only approached 0.5 %, whereas the upper limit suggested in the final product is 2 %. Nevertheless, an additional Ames test for the impurity was deemed unnecessary based on this impurity being a closely-related degradation product of the active substance, and the lack of any additional structural alerts. The very similar chemical structure of the impurity and parent compound was accepted.

User Safety

The user safety assessment submitted in compliance with (EMEA/CVMP/543/03-Final) assessed the pattern of use of the product and some of the key safety features inherent in the product. The biggest "group at risk" is small children and the risk management strategies proposed including the use of child-resistant screw caps. Oral, ocular and dermal exposure were taken into account by the report. Oral LD_{50} values taken from single dose toxicities in mouse, rat and dog, with an additional safety

factor, was used for exposure in children and in the instance of breakage and spillage in adults, as the exposure risk scenario will be acute.

Dermal/ocular toxicity and skin sensitisation studies were performed. Applying EU Directive 67/548, (adapted), the substance would not be classified as irritating/sensitising to the skin or the eye. Taking into account that the product is not irritating or sensitising, risk characterisation was only performed for the oral route. The margin of exposure was calculated for various different scenarios. The data indicate that in case of accidental ingestion in humans, no serious toxicological risk is expected. The CVMP agreed that the risks to users are suitably addressed by the current warnings in the SPC.

Environmental Risk Assessment

The Phase I assessment submitted covered the physico-chemical and pharmacodynamic properties of mitratapide. In addition, the likely pattern of use was discussed. Approximately 85 % of an administered dose is excreted in faeces, while the remaining 15 % is eliminated in urine. Both the parent compound and the various metabolites are potent MTP-inhibitors. The risk assessment concluded in Phase I. A Phase II assessment is not deemed necessary because of the likely pattern of use and restriction to companion animals. No particular environmental concerns are foreseen with this active substance.

Overall Conclusion on Safety

The studies submitted adequately characterised the acute toxicity of mitratapide at dose rates well in excess of the RTD in the dog (0.63 mg/kg BW). In some studies, rats were more sensitive to adverse effects of mitratapide than mice. There were reductions in white blood cell values at high dose rates, and effects on food intake, bodyweight gain and faecal consistency. Mortalities were only reported following IV administration in the rat. The safety margin following acute oral exposure is very high.

A large number of studies that characterised the repeat dose toxicity profile of mitratapide in target and non-target species were presented. In general, mitratapide was well tolerated at the RTD. Significant changes occurring at this dosage level were primarily confined to alterations in serum parameters (phospholipids, cholesterol, triglycerides etc.) and vacuolation/lipid droplet deposition in the intestines and liver. At higher dose rates, mitratapide resulted in soft faeces and decreases in food intake and bodyweight gain. A large number of biochemical values were modified, and not all were considered related to the compounds known mode of action. Total protein, albumin and AP values were reduced in several studies, while potassium values were elevated in others. Organ weight changes were generally confined to relatively high dose rates.

A single generation reproductive toxicity study showed no adverse effects of mitratapide on a variety of reproductive parameters. Copulation rates, fertility rates, the numbers of foetuses and pre- and post-implantation losses were unaffected by treatment. Two GLP-compliant developmental toxicity studies were performed in the rat and rabbit. Although maternal toxicity and reduced reproductive performance were evident at high-dose rates, only minor variations and deviations were detected at dose levels well above the RTD in the dog.

Mitratapide provided negative results in a series of mutagenicity studies. 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. Mitratapide can cause slight irritation to the skin and eyes. However, the molecule did not show any evidence of a skin sensitising potential.

A satisfactory user safety assessment was provided, and addressed the risks to users. Suitable warning statements are included in the SPC. An environmental risk assessment stopped in Phase I which was deemed acceptable.

Pharmacodynamics

Studies conducted showed that mitratapide has an inhibitory effect on the secretion of ApoB from human hepatocytes and this effect is mediated by inhibition of the microsomal triglyceride transfer protein (MTP). The parent compound is extensively metabolised and the principle metabolites possess pharmacodynamic activity. In dogs treated with mitratapide, markedly decreased postprandial serum triglycerides, phospholipids and cholesterol are observed. The accumulation of triglycerides inside the enterocytes - both macroscopically visible as white deposits and confirmed histopathologically - provides additional evidence for the inhibition of MTP. The latter phenomenon is also observed in patients suffering from abetalipoproteina, a disease characterised by absence of MTP. No direct evidence is provided that there is inhibition of MTP at the level of the enterocyte. However, it is accepted that: the demonstration of MTP inhibition in hepatic cells; the effects of mitratapide on postprandial serum triglycerides, phospholipids and cholesterol in the dog; and, the accumulation of triglycerides within enterocytes all suggest that MTP is inhibited at the level of the enterocyte.

The clinical studies conducted showed that the product suppresses appetite. The reduction in appetite is linked to the local mode of action at the level of the gut (inhibition of uptake of dietary lipids and distribution in the enterocytes) which triggers a negative feedback signal on feed uptake.

The findings of a number of studies conducted for the purposes of evaluating secondary pharmacodynamic effects of mitratapide were presented. Mitratapide has been shown to have an effect on the cytochrome P450-dependent reaction involved in the activation and catabolism of vitamin D3. It was concluded that there will be no effect on the activation nor catabolism of vitamin D3 of clinical relevance at the therapeutic dose in dogs. Further evidence is available from the toxicology studies and the Target Animal Safety study where histopathology did not reveal any abnormalities in bones. Furthermore, the risk for vitamin D deficiencies is of relevance in young animals below the age of 1 year but of no clinical relevance in adult dogs. Yarvitan is indicated for use in adult animals only. It is noted that the IC50 values for inhibition of vitamin D3 activation and catabolism were respectively about 13 and 40 times higher than the concentrations needed for effect on MTP.

Decreased serum calcium levels were a common observation in toxicity and tolerance studies in dogs and occurred at the therapeutic dose (0.63 mg/kg) after a prolonged treatment duration of 9 weeks. Mitratapide was shown to reduce serum aldosterone in a dose-dependant manner in rats and may exert a similar effect after long-term treatment in dogs.

Mitratapide is expected to decrease the absorption of lipid soluble vitamins, which could theoretically result in a deficiency. While the absorption of vitamin A and E was somewhat decreased, values never dropped below the lower limit of the normal range. In view of the relatively short treatment duration ("3-2-3" schedule) and the fact that uptake of lipids is not blocked by 100 %, it can be concluded that the effect on the uptake of vitamins A and E is not clinically relevant. The toxicology and efficacy studies did not reveal any bleeding abnormalities nor changes in haematological parameters indicative of a vitamin K deficiency.

It is accepted that there was no clinical or clinicopathological evidence of vitamin D or vitamin K deficiency in any of the studies conducted. Clinically significant reductions in vitamin levels are unlikely to occur with the proposed treatment schedule. Supplementation with vitamins during treatment with mitratapide is therefore not required.

Tolerance in the target species

Numerous changes considered related to the mode of action were detected in the studies and are not considered unexpected/abnormal. These included weight loss, reduced feed consumption and a decrease in serum phospholipids, triglycerides and cholesterol. The significant weight loss is related to the pharmacological activity of the product and reduced feed consumption. It is noted that

administration of the product at 3x and 5x the RTD resulted in very significant weight loss, such that a number of test animals were classified as emaciated. Following cessation of treatment, appetite increased and animals rapidly regained weight. After stopping treatment, feed consumption increased markedly in the treated groups such that it exceeded baseline feed consumption for each group and exceeded feed consumption in the control group. This finding would suggest that while the test product decreases feed consumption, there is a compensatory increase in appetite/demand for food once treatment has stopped. This finding is of relevance to diet/weight control following cessation of treatment in the field setting. Rebound weight gain after stopping treatment is to be expected. As the bodyweight reducing efficacy of mitratapide varies significantly between treated dogs, section 4.5 of the SPC includes a statement that treatment should be also interrupted in case of severe and rapid bodyweight loss.

Treatment with mitratapide had no effect on the various urinary parameters or on ophthalmological findings.

The therapeutic dose of 0.63 mg/kg/day administered continuously for 9 weeks was well tolerated and that in view of the proposed treatment schedule (3-week on, 2-week off, 3-week on), mitratapide can be safely used for the management of canine obesity. It is noted that the design of the treatment schedule allows for any changes in clinicopathological parameters (induced by the first three week treatment period) to correct during the treatment free period, before commencing with the second period of treatment.

It was seen that the concomitant treatments of meloxicam or carprofen with mitratapide did not affect the safety or efficacy profile of the test product and had no influence the bodyweight lowering effect of mitratapide when given simultaneously. The choice of NSAIDs was based on their wide use and availability. ACE-inhibitors e.g. benazepril or enalapril treatment alone had no influence on bodyweight, nor did they influence the bodyweight lowering effect of mitratapide when given simultaneously. It is accepted that the concomitant treatments of benazepril or enalapril with mitratapide did not affect the safety or efficacy profile of the product. The choice of ACE-inhibitors was based on their wide use and availability. However, as with NSAIDs, the conclusions on the safe use of mitratapide together with ACE-inhibitors is based on a limited number of observations in healthy dogs only.

A treatment-related effect, recorded in a number of safety and efficacy studies, was vomiting. Typically, vomiting, when it occurred in treated animals, is mild/moderate in severity, is not associated with signs of systemic toxicity and resolves, despite the continuation of treatment, in most cases. Another adverse effect detected that is most likely linked to the mode of action of the product is occasional/intermittent soft stools or diarrhoea. It is attributed to the physiological shedding of enterocytes, filled with triglyceride-containing lipid droplets, into the faeces.

A number of other treatment-related adverse effects were observed in the pivotal target animal safety study. At the recommended treatment dose with a prolonged treatment duration these included: changes in red blood cell parameters; decreases in albumin, globulin, total protein and calcium; increases in ALT and AST; and, thickening of the wall of the small intestine and the presence of fat deposits on the mucosal surface. Generally, the severity of these effects increased with increasing dose. Increases in ALT and AST were not associated with histopathological degeneration of hepatocytes and were completely reversible within 14 days and no signs of liver pathology were seen at the therapeutic dose level in field studies. In addition, effects on the bone marrow and thymus were evident in the high dose groups. Given that these findings had normalised, or appeared to be reversing, within two weeks of the end of treatment, the CVMP concludes that they are of no toxicological significance.

The SPC includes statements to the effect that anorexia, vomiting and diarrhoea may occur during treatment. In addition, the SPC contains a recommendation that in the event that such effects are significant or occur repeatedly, treatment should be interrupted and the advise of a veterinarian should be sought. This advice/recommendations are considered to be appropriate. In respect of the SPC,

section 4.6, Adverse effects, the frequency of the occurrences of vomiting, anorexia, diarrhoea and weakness (or lethargy) are indicated.

Dose finding study

This study was conducted to determine the lowest effective and safe dose of mitratapide to reduce the bodyweight of dogs to an extent that is clinically relevant. Feed was available *ad libitum* for 3 hours per day. The reduction in weight for the 0.63 mg/kg treatment group was not significantly different to that achieved with higher doses. It was concluded that the final formulation containing 0.63 mg/kg is the preferred dose, as this is the lowest effective dose.

Dose confirmation study

This was a GLP-study conducted with the final formulation using the proposed treatment regimen. Both occasional vomiting and diarrhoea were recorded during the study, but it is noted that there was no clear relationship between treatment and the occurrence of these effects. As mitratapide at a dose of 0.63 mg/kg induced a statistically significant bodyweight loss, it was concluded that the tested treatment schedule is effective and safe to reduce the bodyweight of Beagle dogs.

Laboratory efficacy studies

The various studies conducted showed that a dose of 0.63 mg mitratapide/kg is the optimum dose, in terms of both safety and efficacy, to induce significant weight loss in Beagle dogs fed *ad libitum*. Efficacy is improved when the product is administered with food. In mitratapide-treated animals, bodyweight tends to decrease in a characteristic pattern: most weight was lost in the first three weeks of treatment, weights were maintained during the non-treatment periods and additional weight loss was noted in the second treatment period. Efficacy of the product when administered in accordance with the 3-2-3 treatment schedule is greater than efficacy after a single three week treatment period. Application of a feeding regimen in accordance with energy requirements for maintenance is necessary to prevent rebound weight gain after the first three weeks of treatment. The presence of mitratapide mixed in the feed has a tendency to suppress food consumption. Efficacy of the product is not reduced when dogs are fed more than once a day. The between treatment interval of two weeks was accepted and the ability to leave the dog on its normal diet during the first treatment period is expected to be an advantage in terms of owner compliance.

The appetite decreasing effect is related to the mode of action of the product (inhibition of dietary lipid uptake and distribution in the enterocyte resulting in a satiety signal). It was found that appetite suppression does not occur in dogs treated with mitratapide and receiving a low fat diet. In dogs fed a 22 % fat diet, food consumption was reduced by up to 33.8 %, whereas, in dogs fed a 5.5 % diet, feed consumption was virtually unchanged.

Field trials

Two separate field trials were conducted, one in the EU and the other in the US.

<u>EU Field Trial</u>
The EU study was a multicentre, blinded, randomised, placebo-controlled field trial with two parallel treatment groups with dogs presenting with obesity.

The test animals were administered either the test product (at a dose of 0.63 mg/kg/day = 1 ml/8 kg/day) or the placebo (at a dose of 1 ml/8 kg/day) for three weeks followed by a treatment free period of two weeks followed by a second treatment period of three weeks. After the end of the second treatment period, the dogs were followed for four additional weeks. The daily dose of oral solution had to be mixed into a small portion of feed and presented to the dog to be consumed before allowing the remainder of the meal. The principle breed types included in the study were crossbreeds, Labrador retriever and Golden retriever. The categories of concomitant medications most frequently used during

the study matched the types of drugs most frequently used in current veterinary practice, e.g. vaccines, anthelmintics, ectoparasiticides, systemic antibacterials and anti-inflammatory drugs.

There were no differences between groups with respect to blood biochemistry parameters, with the exception of the expected mitratapide-related reductions in triglycerides and cholesterol. This is noteworthy in view of the fact that mitratapide-related effects on albumin, globulin, calcium, ALP, AST and ALT were detected in a number of the preclinical studies.

When looking at the weight response in individual animals, it would appear that for a proportion of dogs in both study groups (52.3 % and 38.9 % in the placebo and mitratapide groups respectively), bodyweight increased during the day 21 to day 36 non-treatment period. It emphasises the fact that close dietary management is critical in maintaining any reduction in weight gain due to this treatment.

From this European multicentre field study it can be concluded that Mitratapide at a dose of 0.63 mg/kg BW and a 3-2-3 week treatment schedule proved to be more efficacious in reducing body weight in obese dogs when compared to placebo. In clinical trials, the following weight loss percentages were obtained:

Percentages of dogs per weight loss category for mitratapide versus placebo:

	% of treated dogs*	
weight loss category	placebo	mitratapide
≥ 10 %	6.8	25.2
≥ 7.5 %	11.4	41.7
≥ 5 %	22.7	63.8

* : in line with the recommended treatment schedule

- The treatment is an initial measure in an obesity management programme; it has to be combined with individually adjusted dietary measures which have to be continued after treatment termination.
- *There was a high frequency of digestive tract disorders that could be related to treatment, including vomitus, anorexia/decreased appetite, and diarrhea.*
  The following adverse reactions were observed during the clinical trials (pooled data*):

Clinical observation	Mitratapide	Placebo
vomiting : occasional (≤ 3x)	20.0%	5.6 %
vomiting : repeated (> 3 x)	10.0 %	2.2 %
diarrhoea / soft stools	10.0%	4.4 %
anorexia / decreased appetite	17.8%	10.0 %
lethargy / weakness	5.2%	2.2 %

* data from 360 dogs over the whole treatment period.

US Field Trial

The US field trial was a multicentre, blinded, randomised, placebo-controlled field trial with two parallel treatment groups. Dogs presenting with obesity were enrolled in the study over a period of 22 weeks. The principle breed types included in the study were crossbreeds, Labrador retriever, Golden retriever and Dachshund.

Mitratapide treatment caused a significant reduction in weight loss compared to placebo. In the mitratapide group twice as many dogs achieved weight losses in excess of 10 % compared to the placebo group.
In clinical trials, the following weight loss percentages were obtained:

Percentages of dogs per weight loss category for mitratapide versus placebo:

	% of treated dogs*	
weight loss category	placebo	mitratapide
≥ 10 %	9.5	22.5
≥ 7.5 %	11.9	47.3
≥ 5 %	31.0	65.1

* : in line with the recommended treatment schedule

For the mitratapide-treated group, there was a clear decrease over the first 21-day treatment period, with a stable bodyweight between day 21 and 35, followed by a further, smaller decrease in the second treatment period. While it is accepted that there was a significant difference between groups with respect to the primary efficacy parameter, it is noted that the extent of the mean weight loss reduction in both groups was very similar from Day 21 to the end of the study. This would suggest that for some dogs the initial feeding regimen calculation over-estimated the requirements of certain individuals. This emphasises the fact that close dietary management is critical in maintaining any reduction in weight gain due to this treatment. The SPC includes a statement to this effect.

As in the EU study, vomiting, anorexia and diarrhoea were recorded as adverse effects. In respect of blood biochemistry parameters, the only group differences of significance noted were mitratapide-related reductions in triglycerides and cholesterol. For both ALT and AST, there were slight (non-significant) increases at the end of the treatment period and a return to baseline concentrations 4 weeks later.

For both field studies, a significant reduction in weight loss was achieved in treated animals compared to placebo. While the magnitude of the mean weight reduction in treated animals over the total (56 day) treatment period could only be considered a modest reduction (in the range 6-7 %), it is clear when looked at on an individual animal basis that mitratapide treatment provided a clear advantage over placebo. In both the EU and US field studies, the numbers of animals that achieved weight losses in excess of 7.5 % were approximately 4 times higher in the mitratapide group compared to the placebo group. In both field studies, the secondary efficacy parameter 'vitality' was not statistically significantly different between groups. In the US study, the criterion for determining success of treatment was set at a $\underline{\geq}$13 % reduction in relative bodyweight. This was based on published literature where it is documented that obese dogs with hip arthritis significantly improved when relative body weight decreased by 13% or more. In the US study, there was a statistically significant difference between groups with respect to this secondary efficacy parameter.

Published data is available in which the favourable effect of bodyweight reduction achieved with restriction diet in dogs with hind limb lameness is shown. Although a relation of bodyweight and mobility in dogs with osteoarthritis is assumed, the study did not include an evaluation of the condition of the dogs.

The incidence of vomiting in the field trials was different from the incidence in the laboratory studies, where only occasional incidences of vomiting were observed. This suggests that the timing of product administration with respect to feeding may influence the incidence of vomiting: that is, in the laboratory studies, when mitratapide was administered on a full stomach incidence of vomiting was less than that recorded for the field trials, where it was recommended that the product be administered with a small amount of feed before a full meal. A recommendation appears in the SPC about resuming treatment following interruption after a meal, after incidences of vomiting in animals under treatment. As regards the severity of vomitus and the need of treatments, in the EU field trial 17.4% of dogs with vomiting required treatment compared to no control animals, and that most of the premature removal of dogs in this field trial were related to vomitus/decreased appetite that was considered unacceptable by the owners. During the field studies, interruption to treatment and/or a reduction in dose of product administered was permitted where adverse effects (vomiting or anorexia) occurred. This is addressed in the SPC section 4.5.

In the SPC, it is recommended that, at the end of the first treatment period, feeding for maintenance can be achieved either with a regular pet food or with a low calorie (diet) pet food. Mitratapide can be combined with any type of pet food (regular or diet pet food). This was demonstrated in the field trials where mitratapide was used in combination with a large number of commercial dog food brands, including various diet pet foods. The efficacy of Yarvitan was consistent, irrespective of the type of food used. It is expected that diet pet foot will be low calorie and low in fat.

V. RISK BENEFIT BALANCE

Yarvitan contains the active substance mitratapide and is presented as a non-aqueous 5 mg/ml oral solution. The product is packaged in amber glass bottles of 55 ml, 120 ml and 210 ml. The solution is manufactured using a standard manufacturing process involving simple dissolution of the excipients and 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 finished product specification includes tests for active substance content and identity, antioxidant content and identity, chromatographic purity, deliverable volume and microbiological quality. The excipients have been fully characterised. It has been demonstrated that the manufacturing process does not result in an unacceptable change in stereochemical purity and the absence of limits for these impurities on the specification is therefore justified.

No materials of animal origin are contained or used in this veterinary medicinal product. 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 Commission Directive 2001/82/EC as amended.

Stability data under VICH conditions has been presented for three pilot scale batches of product packed in the packaging proposed for marketing. A shelf-life of 2 years for the finished product and an in-use shelf-life of 3 months was accepted based on the data provided. Specifications set will ensure that product of consistent quality will be produced.

The safety studies submitted adequately characterised the acute toxicity of mitratapide at dose rates well in excess of the RTD in the dog (0.63 mg/kg BW). 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. Side effects have been noted during treatment of dogs with Yarvitan. Vomitus was the most frequent one, but anorexia/decreased appetite, which is suggested to be linked to the pharmacodynamic activity of the compound (lipid accumulation in the intestinal enterocytes), has also been noted. Other side effects were related to haematological and blood chemical parameters. The pathophysiology of some of these side effects is still uncertain. Appropriate warnings are included in the SPC.

A single generation reproductive toxicity study showed no adverse effects of mitratapide on copulation rates, fertility rates, the numbers of foetuses and pre- and post-implantation losses. Mitratapide provided negative results in a series of mutagenicity studies. 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.

Mitratapide caused slight irritation to the skin and eyes. However, the molecule did not show any evidence of a skin sensitising potential. A satisfactory User Safety assessment was provided and the user risk management procedures detailed in section 4.5 of the SPC are appropriate.

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

The pharmacokinetic features of mitratapide have been adequately characterised. Mitratapide is rapidly absorbed following oral administration and is extensively metabolised. From the efficacy studies the following points can be made; a dose of 0.63 mg mitratapide/kg is the optimum dose, in terms of both safety and efficacy, to induce significant weight loss in Beagle dogs fed *ad libitum*; efficacy is improved when the product is administered with food; in mitratapide-treated animals, most weight was lost in the first three weeks of treatment, weights were maintained during the non-treatment periods, and additional weight loss was noted in the second treatment period; efficacy of the product when administered in accordance with the 3-2-3 treatment schedule is greater than efficacy

after a single three week treatment period; dietary restriction is necessary to prevent rebound weight gain; the presence of mitratapide mixed in the feed has a tendency to suppress food consumption; and, efficacy of the test product is not reduced when dogs are fed more than once a day.

It is accepted that when the product is administrated in accordance with the label recommendations, weight reduction will be achieved in a proportion of treated dogs. This fact has been confirmed in the pivotal dose determination and dose confirmation studies. In addition, for both field studies, a significant reduction in weight loss was achieved in treated animals compared to placebo. While the magnitude of the mean weight reduction in treated animals (compared to baseline) over the total (56 day) treatment period could only be considered a modest reduction (in the range 6-7 %), it is clear when looked at on an individual animal basis that mitratapide treatment provided a clear advantage over placebo. The inclusion of dogs with health risk factors was not required in the clinical field studies. Moreover, a correlation between obesity and health risk factors has not been demonstrated in dogs.

While it is accepted that obesity is a problem in pets in the Western World and that a reduction in weight in an otherwise obese dog is likely to be beneficial, Yarvitan can offer a benefit over conventional dietary management. In relation to the potential risks for the dog, it is clear that adverse effects (albeit, typically mild and transient) may be associated with treatment at the recommended dose. In addition, there are uncertainties relating to certain effects (for example, on the adrenal glands) and there would appear to be the potential for effects on the availability of fat soluble vitamins and accumulation of lipid in the liver. However, based on the target animal safety data available, the CVMP accepted that when the product is used as recommended, the potential for significant adverse effects to treatment is low. This fact, coupled with the knowledge that there are adequate safety statements in the SPC, that the product will only be available on prescription (that is, a veterinarian will decide whether this product is an appropriate treatment for an individual obese dog) and that animals are only likely to be prescribed the product as part of a weight reduction programme (to be used in conjunction with appropriate dietary changes) where they will be monitored over time, led the CVMP to conclude that the benefit to risk profile could be considered acceptable.

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 Yarvitan were considered to be in accordance with the requirements of Council Directive 2004/28/EC, as amended.