

SCIENTIFIC DISCUSSION

1. INTRODUCTION

Ypozane tablets contain the active substance osaterone acetate and are indicated for the treatment of benign prostatic hypertrophy (BPH) in male dogs. The objective of treatment is to decrease the size of the prostate gland and thus alleviate clinical signs.

BPH is an age related change of the prostate where the prostate increases in size. This increase in size, or hyperplasia, is a non-malignant change that often does not cause clinical problems but can cause signs such as constipation and difficulty in urinating. BPH is the most common disease of the prostate, and occurs in almost all non-castrated male dogs as they age. The increase in size is caused by hormonal changes in the ratio of androgens, like testosterone and estrogens. Many affected dogs act normal, but if there is a large degree of prostatic hyperplasia, a dog might become symptomatic.

The recommended dose is 0.25 – 0.5 mg osaterone acetate/kg bodyweight per day for 7 days. In order to facilitate dosing dogs of different sizes, the tablets are presented in four tablet strengths.

2. QUALITY ASSESSMENT

Composition

Ypozane tablets are uncoated, tablets available in four different strengths (1.875 mg, 3.75 mg, 7.5 mg and 15 mg) to facilitate treatment of dogs of variable bodyweight. Conventional pharmaceutical excipients for tablets are used and full details are included in the SPC.

Container

The tablets are packed into cold formed foil blisters consisting of a composite aluminium strip with a heat sealed aluminium film. Each blister contains seven tablets packaged in an individual carton box.

Clinical Trial Formula

Two different formulations were used in clinical trials. In the pivotal clinical field study, in preclinical studies (pharmacokinetics, target animal safety) and in (supportive) dose determination studies, all strengths of the final tablet formulation were used. However, in the pivotal dose confirmation study and in a second (supportive) field study, osaterone acetate was administered as a suspension in water at a dose rate of 1 ml per 10 kg.

Development Pharmaceutics

The active substance is practically insoluble in water and thus micronised material is used, as small particle size generally enhances absorption of drugs. No specific studies relating to the determination of particle size specification are presented but the product is an immediate release formulation and exhibits rapid disintegration and dissolution. The active substance does not exhibit polymorphism.

The product is manufactured via direct compression and the excipients are all commonly used for this type of process and dosage form. The quality of lactose monohydrate used is one consisting of spherical particles, which flow readily and permit its high compressibility. The shape of the particles is controlled by microscopic examination (Ph.Eur. 2.9.13) and the particle size by sieving (Ph.Eur. 2.9.12).

No details of development studies to select excipients and optimise concentration are presented. However, preliminary characterisation of two batches of each tablet strength demonstrate satisfactory and consistent results with respect to appearance and size, resistance to crushing, mass uniformity, friability, disintegration time and water content. Preliminary stability studies on pilot scale batches up to 6 months at 25°C and 40°C, of all four strengths demonstrate the formulation to be stable with respect to appearance, resistance to crushing, disintegration, water content and assay. Samples for these stability studies were stored in the proposed packaging, thus demonstrating the suitability of the chosen pack, and this is also confirmed in the stability studies presented in Part IIG. Content uniformity in compliance with Ph. Eur. requirements is demonstrated for the 1.875 mg tablet strength (this strength is the only one to contain less than 2 mg of active substance). The batch analysis results presented in section IIF also demonstrate compliance with the Ph.Eur. monograph for uniformity of dosage units.

In vitro bioequivalence between the four tablet strengths has been demonstrated. Dissolution profiles were determined in buffer medium at pH 4.5, pH 6.5 and pH 7.5 according to the Ph.Eur. monograph on dissolution. As could be expected for tablets manufactured from the same percentage formulation, no significant differences between the four strengths are observed. The buffer solution at pH 6 is used for routine analysis. This pH corresponds approximately to that of the duodenum, the primary site of absorption for the molecule. Details of the development and validation of the dissolution method including selection of the medium, paddle speed, discriminatory nature etc, were provided. The use of multiple tablets in individual dissolution vessels was chosen to obtain the same concentration of active substance of 15 µg/ml. However, this does not justify using multiple tablets when performing routine dissolution testing or dissolution testing as part of a stability study. The applicant agreed to carry out dissolution testing using single tablets and to validate the HPLC assay across the necessary range. Validation of the dissolution method was performed and full details provided.

With respect to residual solvents, the daily dose is less than 10 g and so option 1 can be applied. Residual solvents in the active substance are discussed in Part IIC and the only excipient to contain residual solvent is maize starch, which has a limit of 5000 ppm for the solvent acetic acid. This is in line with the VICH limit for class three solvents and is, therefore, acceptable.

Although no specific formulation development studies have been presented, the data provided does demonstrate that the formulation is suitable for its intended use with rapid disintegration times and ready release of the active substance from the formulation.

Method of Preparation

The manufacturing formula for the proposed batch size was presented.

The manufacturing process is a standard one and involves dry blending of the active substance with excipients followed by lubrication, compression and packaging. In-process controls include control of mixing times and appearance, tablet size and weight, hardness, friability and disintegration of the compressed tablets. In order to specify the limits and frequency of testing for the in-process controls of the compression stage, a summary table was supplied. The integrity of the blister pack seals are to be checked during packaging using an immersion test. This test is intended to be a non-routine test performed on 1 in 10 batch following successful validation of the packaging process at full-scale.

Process validation has been carried out on three pilot scale batches. Portions of each of the bulk batches were used to produce each of the tablet strengths. Particle size, apparent density and flowability were determined on the bulk powder batches. Uniformity of mass, tablet size, resistance to crushing, disintegration, friability, uniformity of content, microbiological quality, dissolution and impurity content were determined on the four tablet strengths. Satisfactory results are reported for all parameters and the data provided on impurities demonstrate that the manufacturing process does not lead to an increase in the active substance related impurities when compared to levels present in the active substance raw material itself.

CONTROL OF STARTING MATERIALS

Active Substance

Osaterone acetate is not listed in a pharmacopoeia and a detailed specification was provided including tests for appearance, solubility, identity (chiral), particle size, residual solvents, melting point, loss on drying, impurities and assay. The specification is in-line with general pharmacopoeial principles and the impurity limits comply with VICH requirements for a new drug substance. A tabulated specification for the active substance was provided, detailing test parameters, limits and reference to the methodology used.

Adequate specifications for all raw materials used in the process are provided. Routine in-process controls are included in the detailed description of the manufacturing process provided in the dossier. The specification of the primary starting material consists of appearance, solubility, identification by IR and HPLC, loss on drying, residue on ignition, related substances and assay by HPLC. The last intermediate of the synthesis is considered as a key intermediate and its specification includes limits for appearance, solubility, identification by IR and UV, flame colouration, optical rotation, melting point, individual impurities, total impurities, loss on drying and assay.

Assay and related substances are determined by reverse phase HPLC with diode array UV detection. The methods have been satisfactorily validated in line with VICH guideline GL2 CVMP/VICH/591/98. Residual solvent levels are determined by head space gas chromatography with a capillary column. The method has been satisfactorily validated in line with VICH GL2 CVMP/VICH/591/98. Particle size analysis is carried out by microscopy under polarised light with magnification of 10.

Osaterone acetate is synthesised from 3,20-dioxopregn-4-en-17-yl acetate. The chirality of the active substance is imparted by the starting material and does not change during the synthetic process. Osaterone acetate is freely soluble in chloroform and tetrahydrofuran, soluble in acetonitrile, slightly soluble in methanol and ethanol, very slightly soluble in ether and practically insoluble in water. The melting point is 257°C. Weight change is not more than 0.5 % even after 6 months storage at 40°C/75% RH. In differential scanning calorimetric analysis osaterone acetate showed the sharp endothermic peak derived from the fusion at nearly 259.5°C. In thermal gravimetric analysis no weight change by heating was observed up to 267°C. Partition coefficients are reported on n-octanol and chloroform solutions. Optical rotation values of the chloroform solution are also reported.

Individual impurity levels detected in batch and stability data to date are all below the VICH identification threshold of 0.2 % (CVMP/VICH/837/99).

Details on all the solvents used in the manufacturing process have been provided and class 2 solvents used in the final step of synthesis will be routinely tested in the final drug substance according to EMEA/CVMP/511/03.

Batch data for 5 batches (3 full scale and 2 pilot batches) were presented and considered in compliance with the specification.

Excipients

Conventional pharmaceutical excipients are used and comply with the Ph.Eur. monograph, i.e. pregelatinised starch, carmellose calcium, talc, maize starch and magnesium stearate.

Lactose will be routinely tested for particle size and particle shape, in addition to those parameters listed in its Ph. Eur. monograph.

PACKAGING MATERIAL (IMMEDIATE PACKAGING)

The product is packaged in a cold-formed composite aluminium strip and a heat-sealed aluminium film. Specifications and routine tests for the composite aluminium detailed in the dossier, consist of identification by IR, visual examination, mass per square metre, thickness of film. Specifications and routine tests for the thermo sealable lacquered aluminium foil consist of appearance, identification by IR, presence of the lacquer and thickness of the film.

The composite aluminium foil is certified by the supplier as complying with Ph. Eur. 3.1.11. Materials based on non-plasticised poly(vinylchloride) for containers for dry dosage forms for oral administration. The thermo sealable lacquered aluminium foil is certified by the supplier as suitable for contact with food. Batch data for 1 batch of each component is provided in the dossier. These packaging materials are standard pharmaceutical materials widely used in packaging of solid oral dosage forms.

SPECIFIC MEASURES CONCERNING THE PREVENTION OF THE TRANSMISSION OF ANIMAL SPONGIFORM ENCEPHALOPATHIES

Magnesium stearate and lactose are the only materials potentially of animal origin. Magnesium stearate is of vegetable origin and lactose is sourced from animals fit for human consumption. Suitable declarations are provided by the suppliers and both materials therefore comply with EMEA/410/01-Rev-02. A declaration concerning the compliance of the active substance, osaterone acetate, with the TSE guideline (EMEA/410/01) was provided by the manufacturer of the active substance.

CONTROL TESTS ON FINISHED PRODUCT

Product specification and details of routine tests for control included appearance of packaging, diameter, thickness, average mass, resistance to crushing, disintegration time, identification, content uniformity, assay, microbiological quality, dissolution and blister integrity. The active substance content is controlled to $\pm 5\%$ for all tablet strengths. The mean result of the test for content uniformity is used as the assay value for the purpose of release. The test for content uniformity is carried out according to the Ph.Eur. monograph 2.9.40 - Uniformity of dosage units. A test for dissolution is included in the release specification. The specification is considered suitable for the dosage form.

Control methods

Identification of the active substance is confirmed by concurrence of retention times in the HPLC assay and comparison of the UV absorbance spectrum with that of a reference standard. Assay is determined using the same HPLC method used for determination of the active content of the raw material. The same method is also used for uniformity of dosage units, dissolution and determination of impurities/degradation products. Related substances are determined during stability studies, but not routinely at release. Dissolution testing is carried out according to Ph.Eur. 2.9.3 using the paddle apparatus. Microbiological quality is determined using a pour-plate method. Other test methods employ standard pharmaceutical/Ph.Eur. methodology.

The analytical method for assay determination has been satisfactorily validated with respect to specificity (placebo, dissolution solvent, known related substances, stressed samples and stressed related substance solutions), linearity, accuracy, precision and stability of solutions.

In relation to related substances/degradation products, the method has been validated as a limit test with respect to specificity, LOD and LOQ (signal-to-noise ratio). The dissolution method has been validated with respect to specificity, linearity, accuracy, repeatability for different tablet strengths and stability of solutions. The methodology for determination of microbiological quality has been satisfactorily validated.

Batch data are presented for three batches of each strength. These batches are also used in stability trials and are produced from pilot scale bulk powder blends. The calculated acceptance values (AV) for Uniformity of Content are below 15.0.

STABILITY

Stability Tests on the Active Substance

Stability data were presented for three pilot scale batches stored at 25°C/60% RH (3, 6, 9 and 12 months), 30°C/60% RH (3, 6, 9 and 12 months) and at 40°C/75% RH (3 and 6 months). All parameters remained within specification at all temperatures with no decrease in assay and effectively no degradation detected. A retest period of 12 months was considered to be appropriate.

Stability Tests on the Finished Product

Tests carried out are the same as those for release with the following additional parameters: water content, friability, individual known or unknown impurities and total impurities. Active substance limits are applied to all tablet strengths. Limits for resistance to crushing are widened slightly from those at release in line with stability results to date. Three batches of each tablet strength were placed on stability under VICH storage conditions (25°C/60% RH and 40°C/75% RH). The batches have been produced from pilot scale bulk powder blends. One of the batches was also tested for photo stability. All batches were packaged in the proposed alu/alu blisters.

Parameters and test methods

Test methods and validation for all parameters have been described. Given the number of batches used in the stability study and the fact that all four strengths are compressed from the same granulation, a matrixing system is described in the protocol whereby not all parameters are tested on each strength at each time point. All tests on the specification are carried out on a periodic basis except uniformity of content, which is replaced by uniformity of mass.

Replacement of uniformity of content with uniformity of mass is acceptable for shelf life testing as once uniformity of content is determined at release, it is not a stability indicating parameter.

Results of tests

The stability studies to date demonstrate the formulation to be stable. Some increase in hardness and resistance to crushing is observed which is slightly more pronounced at 40°C. However, no significant change in disintegration, dissolution, friability or water content is observed. Active substance content remains stable with only slight variability. One marginally out-of-specification result was seen for one batch after 6 months at 25°C. However, subsequent time points are within specification and this result is considered anomalous rather than indicative of any degradation. Individual and total related substances above 0.05 % are not detected.

No statistical analysis of the data is presented but given the stability of the active and lack of degradation observed at both temperatures, the proposed shelf life is considered to be supported by the data. The first three full scale batches of each strength will be placed on stability and analysed according to a matrixing scheme, as applied during the stability studies performed on the pilot batches.

The initial and 24 months stability assay results show compliance of the tablets of each strength with the proposed specifications. The stability data presented confirms the stability of the tablets after 24 months storage. All parameters remain well within specification with no significant changes observed. Results as mg/tablet will be reported at the 36 month stability time point.

The proposed shelf life of 36 months with no specific storage precautions was accepted.

CONCLUSION ON QUALITY ASSESSMENT

Ypozane contains the active substance osaterone acetate and is presented in four tablet strengths containing 1.875 mg, 3.75 mg, 7.5 mg and 15 mg of osaterone acetate, respectively. All four tablets are compressed from the same granulation to facilitate dosing animals over a range of bodyweights. The product is packed in composite aluminium foil blisters and is presented in cartons containing 7 tablets.

The tablets are manufactured using conventional direct compression processing technology. The process itself is adequately described within the dossier with appropriate in-process controls detailed. Some process validation data for pilot scale batches are provided and are considered satisfactory. Validation of full scale batches will be carried out post authorisation.

Full details in relation to manufacture of the active substance, osaterone acetate, were provided. Impurities are controlled in line with VICH Topic GL10 - Impurities in New Veterinary Drug Substances.

The release finished product specifications include tests for active substance content and identity, related substances, average tablet mass, tablet dimensions, resistance to crushing, disintegration, dissolution and blister integrity. Friability and hardness of the tablets are in-process controls. Microbiological quality is reported for three batches of each strength and is included on the specification as a non-routine test. Related substance limits are in line with VICH GL11 requirements with respect to reporting levels. Analytical methods and validation for the finished product are generally considered acceptable and in line with VICH GL 2. Batch data are in accordance with the specification and show uniformity from batch to batch.

The stability of the active substance has been demonstrated with real time and accelerated studies supporting the proposed 12-month re-test period.

The shelf life specifications for the tablets are similar for release, although limits for water content, friability and impurities are introduced.

Stability data at 25°C/60%RH (24 months) and 40°C/75%RH (6 months) have been presented for three pilot scale batches of product packed in the packaging proposed for marketing. The product has been demonstrated to be extremely stable and the proposed shelf life of 36 months, with no specific storage precautions, is supported by the data presented.

3. SAFETY ASSESSMENT

TOXICOLOGICAL STUDIES

Single dose toxicity

A number of GLP compliant studies were performed in mice, rats and dogs, using different routes of administration (oral, subcutaneous or intraperitoneal). Osaterone acetate induced CNS disturbances, vomiting and lethality in various species. Osaterone acetate was more toxic by the oral route than the subcutaneous route. However, the dose rates required for such effects were several multiples of the recommended daily dose of 0.25 – 0.5 mg/kg bodyweight in the dog, e.g. the LD₅₀ after oral use in male dogs was more than 2000 mg/kg bodyweight. In some studies, females were more susceptible than males.

Repeated dose toxicity

The applicant provided a number of well conducted GLP compliant studies investigating the repeat dose toxicity of osaterone acetate in rats and dogs.

In rats, three repeat dose studies were presented; over 1 month (doses of 0 to 500 mg/kg bodyweight), 3 months (doses of 0 to 50 mg/kg bodyweight) and 1 year (doses of 0 to 10 mg/kg bodyweight). Tests involved 10-15 animals per sex and dose group. Osaterone acetate was administered via water. In dogs, four repeat dose studies were presented; one study of 1 month (doses of 0 to 100 mg/kg bodyweight), two studies of 3 months (doses of up to 10 mg/kg bodyweight) and a study of 12 months with a 13 week recovery period (doses of up to 2.5 mg/kg bodyweight). Tests involved 2 dogs per sex and dose group. Osaterone acetate was administered as a gelatine capsule.

For rats, based on the results of the 3-month study, an oral NOAEL value of 0.00625 mg/kg bodyweight was obtained. However, in the 1 year rat study, effects were already observed in the lowest dosage group used (0.08 mg/kg) and no NOEL could be established. In dogs, NOEL values could not be established since effects were observed in all doses tested i.e. from 0.01 mg/kg (3 months). However, it was noted that dogs in this study remained in good health and appeared clinically unaffected by the changes in organ weights/plasma biochemistry.

At lower dose rates (i.e. less than 10 mg/kg bodyweight), osaterone acetate was relatively well tolerated in both species, the only clinical signs reported were gastrointestinal in nature. In dogs and male rats, food intake and bodyweight gain was reduced; however, sex-differences in food intake/bodyweight gain were restricted to rodents and not observed in the target species. At high dose rates, osaterone acetate gave rise to severe neurotoxicity. Convulsions and muscle rigidity were noted in rats treated with 500 mg/kg or more and in dogs, ataxia and tremors were evident at dose rates of more than 10 mg/kg bodyweight.

The target organs for toxicity are similar in dogs and rats and concern mainly the reproductive organs in males (atrophy of testes, epididymis, seminal vesicles, prostate gland) and females (endometrial and uterine gland hyperplasia, reduced corpora lutea). However, other target tissues identified in the repeat dose studies included the liver, kidneys, heart, adrenals, thymus and pituitary gland. Some of the changes were at least partially reversible when medication was ceased.

Osaterone acetate had a weak effect on the mammary gland proliferation in rats and dogs, particular in females with a NOEL for mammary gland proliferation in male and female dogs of 100 mg/kg/d and 0.1 mg/kg/d (1 month), respectively. Based on the results of the tolerance studies and the field studies and taking into account known effects of other compounds of the same chemical class (progestins), the CVMP concluded that osaterone acetate when used at the therapeutic dosage might be involved in mammary gland proliferation. Appropriate reference has been made in the SPC and product literature.

Studies on the effects on reproduction

The Applicant provided two GLP-compliant studies investigating the effects of osaterone acetate on reproduction. In one study, 0.3, 3 or 30 mg osaterone acetate /kg bodyweight was administered to female rats prior to and in the early stage of pregnancy and to male rats from 61 days prior to mating and through the mating period.

Treatment with osaterone acetate resulted in numerous adverse effects on various fertility indices (oestrus cycle, length of the sexual cycle, copulation/fertility indices), particularly at dose rates from 3 mg/kg bodyweight. Differences were noted in food intake and body weight gain between males and females. At the lowest dose tested (0.3 mg/kg bodyweight) there was a reduction in sperm count in males and a significant increase in the duration of dioestrus in females. Besides these latter findings, there were no other significant abnormalities recorded at this dose rate. The NOEL for systemic toxicity and embryo toxicity was, therefore, set at 0.3 mg/kg bodyweight.

In a second GLP-compliant study, 0.12, 0.6 or 3 mg osaterone acetate /kg was administered to female rats 14 days prior to mating and during mating and up to day 7 of gestation and to male rats from 63 days prior to mating and through the mating period.

In general, osaterone acetate exerted only minimal effects on key reproductive parameters such as number of days to copulation, copulation rate, pregnancy rate etc. However, abnormalities relating to oestrus cycle activity were noted at dose rates from 0.6 mg/kg bodyweight, and the birth rate was reduced in high-dose F1 progeny. Although the study design would not meet current VICH criteria, the NOEL for systemic toxicity from this study can be set at 0.6 mg/kg bodyweight for females and 3.0 mg/kg for males, while a NOEL of 0.12 mg/kg bodyweight can be retained for reproductive toxicity.

The CVMP concluded that osaterone acetate exerts several detrimental effects on reproductive function in males and females. However, since the product is not used in female animals and clinical studies in dogs did not reveal any negative impact on semen quality (as observed in rats), the CVMP concluded that no special warning in dogs is needed.

Embryotoxicity/foetotoxicity, including teratogenicity

The applicant provided three GLP compliant studies investigating developmental toxicity of up to 30 mg osaterone acetate /kg bodyweight during the period of organogenesis (rats, rabbits) and during the perinatal and lactation period (rats). In addition, a supplementary non-GLP compliant study was provided on effects in the early stage of gestation (rats).

In rats, foetal observations in F₁ pups revealed no product-related effects or increase in the incidence of visceral or skeletal anomalies. F₁ dams had slightly reduced fertility during their first mating period. In rabbits, systemic signs of toxicity were observed, including neurological signs and effects on food intake/bodyweight gain. A dose-dependent decrease in implantation rates in treated dams did not attain statistical significance. Based on the results of this study, NOELs of 0.14 mg/kg bodyweight and 2.5 mg/kg could be established for teratogenicity in rats and rabbits, respectively.

In rats dose rates from 0.9 mg/kg (and in particular, the high dose of 10 mg/kg) exerted numerous effects on viability, bodyweight gain and reproductive development. However, perinatal development did not appear to be adversely impaired at dose rates less 0.3 mg/kg bodyweight.

The CVMP noted the developmental lesions present at mid- (≥ 0.83 mg/kg bw) and high- (15 mg/kg bw) -dose rates in rats and rabbits, respectively. However, NOELs of 0.14 mg/kg and 2.5 mg/kg bodyweight for teratogenicity could be established in both species. Since the product is only intended for use in male dogs, the CVMP agreed teratogenic concerns in the target species do not arise based on the pattern of use. However, a warning was included in the SPC and product literature that women of child-bearing age should avoid contact with the product or wear disposable gloves, when administering it.

Mutagenicity

Mutagenicity was investigated *in vitro* (bacterial reverse mutation test in *Salmonella typhimurium*; chromosome aberration test with Chinese hamster lung fibroblasts) and *in vivo* (micronucleus assay in mice). The submitted tests were GLP-compliant and in accordance with VICH guidance. The data do not indicate any mutagenic potential for osaterone acetate. The CVMP concluded that no evidence of mutagenicity was identified in a series of studies conducted according to the relevant guidelines.

Carcinogenicity

The applicant submitted a number of GLP-compliant carcinogenicity studies conducted over 13 weeks (mice, rats), 18 months (mice) and 24 months (three studies in rats).

In male mice, a significant increase in alopecia was observed in all treated groups (0, 2.4, 12 and 60 ppm). A significant increase in pancreatic endocrine tumours was noted at the highest dose (60 ppm). However, a NOEL of 12 ppm (approx. 1.43-1.68 mg/kg bodyweight) was retained for carcinogenicity in this species.

In rats, three carcinogenicity studies were conducted over 104 weeks. In the first study using dose rates of 0, 6, 30, 150 ppm, an increased incidence of mononuclear cell leukaemia (MCL) and phaeochromocytoma was noted in F344 females treated at 150 ppm (approx. 7 mg/kg bodyweight), while a non-dose dependent increase in hepatocellular adenomas was noted in males. Two further studies were conducted in female rats (one using F344 rats and the second using both SD and ACI/N strains) with 150 ppm osaterone acetate. The additional studies did not reveal any evidence for oncogenesis and there was no significant increase in the incidence of MCL or phaeochromocytoma.

The CVMP noted that mononuclear cell leukaemia is a common finding in chronic/carcinogenicity studies using F344 rats. Evidence of an isolated, non-reproducible increase in a single test group of female rats only, indicates that this finding is not biologically significant in terms of both user and target species safety. Taking into account that the product will only be administered to male dogs for 7 consecutive days, at intervals of several months, (as compared to the 104 week administration in female rats), the CVMP concluded that NOELs for carcinogenicity of 12 ppm (approx. 1.43 - 1.68 mg/kg bodyweight) and 30 ppm (approx. 1.31 mg/kg bodyweight) could be retained for the mouse and the rat, respectively. Both doses are above the recommended daily dose of 0.25 – 0.5 mg osaterone acetate in the dog.

Sensitising potential

The Applicant provided the results of two GLP-compliant studies investigating the sensitising potential of osaterone acetate administered subcutaneously and intravenously (guinea pigs) or intraperitoneally (rat, mouse). Osaterone acetate treated guinea pigs did not show any reactions while the positive control group (Bovine Serum Albumin (BSA) treated animals) recorded maximum reactions. All treated mice, whether considered more sensitive to bovine globulin or ovalbumin, failed to mount an IgE antibody response within 35 days of multiple test article administration. Based on the results obtained, the CVMP concluded that osaterone acetate was not a sensitising agent in laboratory animal studies.

Observations in humans

The Applicant provided two studies investigating the effects of a single dose of osaterone acetate (10, 15, 20 or 40 mg per person) in human (male) volunteers, one study in healthy men and a second study in men with benign prostate hypertrophy. Both studies had similar results. Administration of single doses of osaterone acetate did not produce overt physical signs of toxicity. However, a significant decrease was recorded in all doses in sex steroid concentrations (plasma FSH, LH, testosterone, oestradiol).

User Safety

Both, professional users (veterinarians and veterinary assistants) and non-professional users (pet owners and other persons/children in contact with the animal) might be exposed to the product. Potential routes of exposure are skin contamination, oral exposure (hand-to-mouth contact), accidental ingestion (e.g. by a child) when administering the product.

The CVMP considered the risk associated with skin contamination to be low due to the lack of sensitising properties of osaterone acetate. Oral exposure by hand-to-mouth contamination was also considered of low risk in view of the NOAEL of 40 mg per adult person (oral).

However, due to the teratogenic potential of osaterone, any contact with osaterone by pregnant women (skin contamination or hand-to-mouth contact) was considered a potential risk. A warning has, therefore, been included in the SPC and product literature that “Women of child bearing age should avoid contact with, or wear disposable gloves, when administering the product.”

Accidental ingestion of osaterone (e.g. a full packet of tablets ingested by a child) could lead to toxicity. However, the blister packets contain several safety features and thus the potential ingestion of 7 tablets would be a rare event. In addition, considering the LD₅₀ values and clinical signs reported in the acute oral toxicity studies in animals, any poisoning is likely to be restricted to transient hormonal perturbations, gastrointestinal or neurological signs. The CVMP, therefore, concluded that the risks posed for children have been adequately addressed by appropriate warnings in the SPC, labelling and package leaflet.

Environmental Risk Assessment

An Environmental Risk Assessment (Phase I) was performed in compliance with the relevant VICH guideline. The product will only be used in a non-food producing animal species and will only be used to treat individual animals. In accordance with the VICH Topic GL6 (Ecotoxicity Phase I) Guideline on Environmental Impact Assessment (EIAs) for Veterinary Medicinal Products – (CVMP/VICH/592/98-final), a Phase II environmental risk assessment was, therefore, not required.

As the product will be used in individual dogs only and treatment is of short duration and infrequent, the product is unlikely to modify the “hormonal activity” of natural substances already present in the environment. Therefore, the CVMP concluded that the use of YPOZANE would not cause an unacceptable environmental risk.

CONCLUSION ON SAFETY ASSESSMENT

In single dose toxicity studies, osaterone acetate induced CNS disturbances, vomiting and lethality in various species. However, the dose rates required for such effects were several multiples of the recommended daily doses in the dog. Osaterone acetate was more toxic by the oral route than the subcutaneous route. In some studies, females were more susceptible than males.

A large number of GLP-compliant studies investigating the repeat-dose toxicity (4 weeks to 1 year) of osaterone acetate in the rat and dog were presented. Although numerous adverse effects were observed, some studies employed extremely high dose rates and/or long periods of administration. At high dose rates, osaterone acetate gave rise to severe neurotoxicity. In addition, gastrointestinal signs were noted in the target species. At lower dose rates, osaterone acetate was relatively well tolerated in both species. There were numerous differences (food intake, bodyweight gain, organ weights etc.) between the two sexes, some of which were predictable given the pharmacological nature/activity of the drug. While numerous findings were reported on haematology, biochemistry and urinalysis, it was hard to establish consistent patterns that were dose-dependent and reproducible between studies. Effects on electrolytes and adrenal hormone concentrations were also evident. The anti-androgenic and progestogenic effects of osaterone acetate accounted for many of the findings observed on necropsy and histopathology. Atrophy of the prostate, gonads and other accessory sex glands was routinely

reported. Other target tissues identified included the liver, kidneys, adrenals, thymus, pituitary gland and mammary glands.

Osaterone acetate exerts several detrimental effects on reproductive function in males and females. This finding was considered predictable in terms of the molecule's pharmacological mode of action. Although developmental lesions were present at mid- and high-dose rates in rats and rabbits, NOELs for teratogenicity could be established in both species.

A battery of GLP-compliant mutagenicity studies was submitted. The data available do not indicate any mutagenic potential for osaterone acetate. Carcinogenicity studies were conducted in both the mouse and rat. A significant increase in pancreatic endocrine tumours was noted at the highest dose tested in male mice. However, a NOEL of 12 ppm (approx. 1.43-1.68 mg/kg bodyweight) was retained for carcinogenicity in this species. Three carcinogenicity studies were conducted in the rat. In the first study, an increased incidence of MCLs and phaeochromocytomas was noted in F344 females treated at 150 ppm, while a non-dose dependent increase in hepatocellular adenomas was noted in males. Two further studies in females (one using F344 rats and the second using both SD and ACI/N strains) did not reveal any significant increase in the incidence of MCLs or phaeochromocytomas. NOELs for carcinogenicity could be retained for both the rat and mouse; both were above the RTD in the dog.

Osaterone acetate was not a sensitising agent in laboratory animal studies. The user safety risk assessment addressed various exposure scenarios relating primarily to non-professional users. It was concluded that the risks posed, particularly for susceptible sub-groups such as children and women of child-bearing age, could be adequately addressed by appropriate warnings in the SPC and package leaflet.

An environmental risk assessment was provided. As the product is intended solely for use in companion animals, the assessment stopped at Step 3 of the Phase I decision tree.

4. EFFICACY ASSESSMENT

PRECLINICAL STUDIES

Pharmacodynamics

The applicant provided results from a number of well-conducted studies in rats and dogs investigating the effect of osaterone on various organs. Two well-known anti-androgens, chlormadinone acetate (from which osaterone is synthesised) and cyproterone acetate were used as positive controls in a number of the pharmacodynamic tests.

Osaterone is a steroid chemically related to progesterone. Both osaterone and its major metabolite (15 β -OH-osaterone acetate) are pharmacologically active with potent anti-androgen activity.

In rats and dogs, oral osaterone induced a dose dependent decrease in the weight of the prostate gland and accessory glands. In rats, osaterone markedly suppressed the growth of pre-existing prostatic tumours. The effect of osaterone on prostatic weight is due to the inhibition of testosterone uptake into prostatic cells. The anti-androgenic effect of osaterone is due to the inhibition of the androgen-receptor complex in a concentration dependent manner.

A transient decrease in serum testosterone concentrations was observed in rats and dogs. It is suggested that this effect may be due to an anti-gonadotropic activity on the hypothalamus and pituitary secretion of LH. However, the effect is less marked than that of some other anti-androgens, and is not expected to have any effect on male sexual function.

In rabbits, pretreated with oestradiol, there was a potent progestational effect. Doses of 0.0025 mg/kg osaterone resulted in endometrial growth. The main metabolite showed no progestational activity. In female rats, osaterone had a significant anti-estrogenic effect.

Osaterone acetate has low affinity with glucocorticoid receptors. However, the metabolite PB-4 (11-OH) might cause transient adrenosuppressive effect (*see also Target animal tolerance*). In dogs, a transient decrease of plasma cortisol was noted during treatment with 0.5 mg osaterone/kg/day. Osaterone acetate did not show mineralocorticoid activity.

No significant secondary effects were observed on the CNS, gastric mucosa, platelet function, respiratory, cardiovascular, autonomic nervous, digestive or urinary systems. Studies were carried out using mice, rats, cats and dogs with osaterone acetate and metabolites at a variety of doses and routes of administration up to 100 mg/kg.

Pharmacokinetics

Pharmacokinetic studies have been conducted in male mice, rats and dogs. Studies in dogs were well conducted and in accordance with the Guideline for the conduct of pharmacokinetic studies in target animal species (EMEA/CVMP/133/99). Osaterone was administered with or without food.

Absorption

In male rats following intravenous and oral administration, absorption was greatly affected by the first pass effect. Bioavailability of osaterone acetate after oral administration was therefore low, around 30%, compared with metabolites. The main site of absorption is the duodenum. The pharmacokinetics are linear for oral doses up to 1 mg/kg.

In dogs, osaterone is rapidly and extensively absorbed and undergoes a first pass effect. C_{max} after oral administration of 0.25 mg osaterone acetate/kg without food or with food was about 60 and 62 ng/ml, respectively. However, because of a great interanimal variation no clear conclusion on the effect of fasting on bioavailability could be shown. The tablets may, therefore, be given with or without food.

Distribution

In rats, both the parent compound and the main metabolite are rapidly distributed to most tissues including the CNS. After repeated administrations, a plateau was reached in most tissues after the third administration; in fat concentrations accumulated and continued to increase slightly to the 21st administration.

In vitro osaterone acetate was highly plasma protein bound mainly to albumin (rats 90-95%; dogs 87 - 92%; humans 93 - 98%). The main metabolite is also highly protein bound but to a lesser extent. Protein binding is reversible and unaffected by other protein bound substances such as diazepam or phenylbutazone and no interactions with such substances are expected.

Metabolism

Generally, steroid hormones are metabolised by oxidation by cytochrome P₄₅₀ in the liver. The effect of osaterone acetate on hepatic drug metabolising enzymes has been investigated in rats at doses up to 32 mg/kg/day for 21 days and in dogs at doses of 0.1, 1.0 and 10 mg/kg/day for 3 months. In both species, high doses (>8 mg/kg) caused a temporary induction of metabolising enzymes.

Fifteen metabolites have been isolated from urine, faeces and bile of several different species. There are species and gender differences in the relative quantity of the various metabolites. The main metabolite is hydroxylated and like the parent compound has anti-androgenic effect. It was found in higher concentration than the parent compound in plasma. In females metabolism is much less extensive. More than 90% of the radioactivity in plasma was due to unchanged compound.

Elimination

In rats, elimination from tissue was rapid in the first 24 hours and then it slowed down. In male rats and mice 80 – 90% of administered osaterone was excreted in faeces via bile and less than 10% in urine. In faeces, most was excreted as conjugates. By contrast, in females most was excreted as unchanged compound. Mean half-life (T_{1/2}) is approximately 17 hours. Urinary and faecal excretion of osaterone acetate and its main metabolite was not affected by repeated administration. In female rats, osaterone acetate is excreted in milk.

In dogs osaterone is relatively slowly excreted with a mean half-life (T_{1/2}) of approximately 80 hours and can be found in faeces and urine up to 14 days after a single dose. After oral administration, excretion via the faeces is about 60% and about 24% via urine.

After repeated administration of osaterone acetate to dogs at 0.25 mg/kg/day for 7 days, accumulation has been observed with a factor of accumulation of about 3-4 without change in the rates of absorption or elimination. Fifteen days after the last administration the mean plasma concentration is about 6.5 ng/ml.

TOLERANCE IN THE TARGET ANIMAL (DOGS)

Target animal tolerance was investigated in three studies conducted in Japan and France. The pivotal study was conducted in 2004 in France according to GLP and the CVMP Guideline for the Evaluation of the safety of veterinary medicinal products for the target animals.

Male beagles aged 12-15 months were treated with 0, 0.25 mg, 0.75 mg or 1.25 mg osaterone acetate/kg, i.e. with 1x, 3x or more than 5-times the recommended minimum daily dose. Treatment was administered as tablets with food once a day for 10 days and this was repeated following a wash out period of 21 days. Parameters were clinical observations, haematology, biochemistry and necropsy at Day 42. In general, the treatment was well tolerated without any impact on clinical signs, bodyweight and haematology. However, a reduction in serum cortisol, a reduced responsiveness to ACTH stimulation testing and - especially in the highest dose group - a decrease in LDH was noted. Post-mortem results indicated a significant decrease in prostate weight and atrophy of glandular

epithelium with hyperplasia of stroma and interstitial connective tissue was seen histopathologically in all treated dogs. A dose related decrease in adrenal weight without morphologic changes was noted in dogs receiving 3x and 5x the recommended dose. Changes associated with adrenal and prostate glands are considered to be related to treatment but not a manifestation of toxicity.

A warning has, therefore, been included in the SPC and product literature that appropriate monitoring should be implemented in dogs under stress (e.g. post-operative) or those with hypoadrenocorticism. The response to an ACTH stimulation test may also be suppressed for several weeks after administration of osaterone.

In field studies, the most commonly observed side effects were related to the progestational effects e.g. increased appetite and behaviour modifications. Transient increases in liver enzymes were noted in dogs with a history of liver disease. However, no evidence of hepatopathy was observed in repeat dose or tolerance studies in healthy dogs when recommended treatment dose was used and the lowest toxic dose affecting the liver in the dog was 10 mg/kg in a 1 month study. In view of the results from the field studies and in absence of particular safety studies, which investigated liver toxicity in dogs, the CVMP concluded that a warning should be included in the SPC and product literature to use the product with caution in dogs with history of liver disease.

In a laboratory study, mammary gland hyperplasia was seen in male dogs as a very rare adverse effect of osaterone. Appropriate warnings have been included in the SPC and the package leaflet.

Semen quality was reported to be adversely affected in some field reports; however, analysis of findings from two other studies, including one GCP study with a follow up period of 135 days following treatment, showed no variation from normal parameters. The CVMP, therefore, concluded that there is no evidence that treatment with osaterone leads to any adverse effect on semen quality in dogs and a warning against use in breeding dogs was not considered necessary.

CLINICAL STUDIES

Dose determination

The Applicant provided a number of non-GLP compliant dose determination studies conducted in Japan, which suggested an effective dose of 0.25 to 0.5 mg/kg bodyweight. Some animals showed an increase in liver enzymes. However, the study design was not satisfactory and the studies could only be considered supportive.

The **pivotal dose determination study** was a multicentre, double blinded, randomised GCP compliant study conducted in France (2003-04) involving 10 veterinary practices.

The study included male adult dogs (3- 15 years, 4.5 – 57 kg bodyweight) from various breeds with BPH, with or without clinical signs, diagnosed by rectal examination or radiography and confirmed by ultrasound examination. Exclusion criteria were prostatitis, hepatic or renal insufficiency, hormonal treatment in previous 2 months, bulldogs and Scottish terriers (with physiological prostatomegaly).

At each site, dogs were randomly distributed to 3 groups treated with 0.125 mg, 0.25 mg or 0.5 mg osaterone acetate /kg. Osaterone acetate was administered as a suspension in water, 1 ml per 10 kg, orally (directly into mouth) once daily for 7 days, during the ½ hour before or after a meal. Dogs were clinically examined every week (Day 0, 7, 14, 28) and the prostate was checked by ultrasound on Day 0, 7 and 14. Efficacy criteria were the (reduced) size of prostate volume at day 14, and as a secondary criterion the time course of prostatic volume or other clinical scores.

A significant reduction of prostate volume of 40.36% and 44.83% was noted at day 14 in the two higher dosage groups of 0.25 mg and 0.5 mg/kg/day, respectively; treatment with 0.125 mg/kg was significantly less effective (26.94%). There was no significant difference between the groups for the secondary efficacy criteria or safety criteria.

Some dogs in each group showed adverse events, i.e. transient increase in appetite or thirst, behavioural changes (less aggressive or more sociable) and vomiting.

The CVMP concluded that the results of this study confirmed a therapeutic dose of 0.25 mg osaterone acetate/kg/day for 7 days. It was noted that osaterone acetate was administered as an oral solution (and not as a tablet) achieving a more exact dosing per kg bodyweight. In view of a possible dose range when using tablets, a dose of 0.25 – 0.5 mg / kg was considered justified.

Two dogs in the lowest dose group died due to cardiac death and acute pulmonary oedema, respectively. These deaths were considered unlikely to be related to the treatment. Since osaterone has weak glucocorticoid action, the theoretical possibility of increased risk for dogs with congestive heart failure was considered in the initial assessment. However, as no similar reactions were seen in the higher dose groups, or other studies conducted in dogs, it was concluded that there was no discernible risk.

Field trials

The applicant provided results of two GCP-compliant field trials investigating the clinical efficacy and tolerance of 0.25 mg osaterone acetate/kg bodyweight per day for 7 days. One of these was conducted with the final (tablet) formulation, in the second trial a suspension of osaterone acetate was used.

The **pivotal field study** was a multicentre, controlled and randomised GCP-compliant study involving 60 veterinary practices in France, Germany, Spain and Romania. The study included a large number of entire male dogs, aged 9 months to 16 years, 3 – 80 kg bodyweight with clinical signs of BPH and increased prostate volume, diagnosed by rectal examination and confirmed by ultrasound examination. Non-inclusion criteria were prostatitis and other prostatic disease, hepatic or renal insufficiency or hormonal treatment in previous 3 months; however, the study included some dogs with BPH associated with prostatitis.

Dogs were randomly assigned to either oral treatment with different strengths of the final formulation (tablets) at the recommended dose of 0.25 mg osaterone acetate/kg bodyweight or to treatment with a positive control, i.e. an intramuscular or subcutaneous injection with delmadinone acetate, a product authorised within the EU for the treatment of BPH. Tablets were administered during the ½ hour before or after a meal, once daily over 7 days. The actual administered dose ranged from 0.25 to 0.5 mg osaterone/kg bodyweight. Delmadinone acetate was administered in the highest recommended therapeutic dosage of 3 mg/kg bodyweight.

At Day 0, 14, 60, 120 and 180, dogs were clinically examined including rectal, ultrasound and bodyweight check. Efficacy criteria were the percentage of dogs with clinical recovery at day 14 and as secondary criteria the percentage of dogs with reduction of prostate volume at day 14, the probability of recovery over time, the time course of prostatic volume between days 0 and 180, and the retreatment time (= time between day 0 and day of relapse, or day 180 if there was no relapse).

Results demonstrated no significant difference between the numbers of dogs with clinical recovery at day 14 treated with osaterone acetate (49.3%) or with delmadinone acetate (47.8%). Prostatic volume decreased in both groups, however, the decrease was greater in the osaterone group (38.03%) than in the delmadinone group (27.56%). There was no statistical significance between groups concerning the probability of recovery over time and the time course of prostatic volume between days 0 and 180. The mean time at which retreatment was required was at least 161 days. About 84% of dogs recovered during the follow up (no difference between groups). Relapse later occurred in some dogs treated with osaterone acetate (16.1%) or with delmadinone acetate (20.7%). There was no statistically significant difference between groups.

Adverse reactions were noted in both treatment groups and were transient and not serious. There were no significant differences between adverse events related to treatment with osaterone acetate (36.7%) or delmadinone acetate (31.2%). The main reactions were increased appetite (22.8%) and behavioural changes e.g. more sociable, more active, hypersexual, anxious (8.9%). Other adverse reactions (less than 4%) concerned gastrointestinal signs such as vomiting or diarrhoea, lethargy, anorexia, alopecia and feminisation.

Some dogs were treated concomitantly with antibiotics to treat prostatitis, however, when these dogs were excluded from the analysis, the benefits of osaterone in treatment of uncomplicated BPH were still clear. The CVMP considered that pre-existing BPH predisposes to prostatitis and that it is common veterinary practice to administer an anti-androgen with antimicrobial treatment in prostatitis cases. The Committee agreed, therefore, that the product could be administered concurrently with antimicrobials in cases of BPH associated with prostatitis.

The CVMP noted that the actual dose administered in many dogs ranged from 0.25 to 0.5 mg/kg bodyweight and was considerably higher than the initially proposed target dose of 0.25 mg/kg. This was due to the administration of whole tablets of a particular strength per weight range group. Dogs in the lower limit of the weight range received a dose of up to 0.5 mg/kg whereas animals in the upper limit of the weight range received a dose of 0.25 mg/kg. However, in view of the tolerance data demonstrating good tolerance of a dose of 1.25 mg/kg/day for 7 days (i.e. up to 5-times the minimal dose), the Committee agreed that the recommended dose should be stated as a range of 0.25 to 0.5 mg per kg bodyweight/day, with the dose not to exceed the recommended maximum dose.

The Applicant also submitted the results of a **second** multicentre, controlled and randomised GCP-compliant study conducted in 2003-2005 in 14 veterinary practices in France, involving 57 male adult dogs, 3.8 – 58 kg bodyweight, with BPH. However, the study did not use the final (tablet) formulation but an oral suspension of osaterone acetate in water. Dogs were allocated to treatment with either osaterone acetate or a positive control, delmadinone acetate. The study design was similar to the trial using tablets.

Study results also were similar to the results of the tablet study. Mean prostatic volume decreased in both groups with a significant reduction of prostate volume at day 14 of 23.37% in the osaterone and 25.98% in the delmadinone group. There was no significant difference between groups on the time course of the mean prostate volume, but there was a significant prostate volume reduction between Day 0 and Day 180. The mean clinical score decreased rapidly between days 1 and 14 (i.e. the clinical condition improved) and continued doing so to Day 120. Clinical cure occurred in 91.3% of dogs in the osaterone group and 88% dogs in the delmadinone group; there was no statistically significant difference between the groups. Adverse reactions occurred in 20.7% dogs treated with osaterone acetate (29.6% for delmadinone) and were generally transient. Main adverse reactions were increased appetite and behavioural changes.

Based on the results of the pivotal and supportive studies, the CVMP concluded that osaterone acetate is as efficacious as another product authorised in the EU (delmadinone acetate) and is similar in its safety profile. A clinical response to treatment is usually seen within 14 days and persists for at least 5 months after treatment. It is, therefore, recommended to re-evaluate the dog 5 months after treatment, and to re-treat if necessary. Appropriate recommendations are included in the SPC and product literature.

CONCLUSION ON THE EFFICACY ASSESSMENT

Osaterone is a steroid chemically related to progesterone. Both osaterone and its major metabolite are pharmacologically active with potent anti-androgen activity. Osaterone acetate also expresses some progestational and glucocorticoid effects.

Osaterone is rapidly and extensively absorbed and undergoes a first pass effect. Administration with food tends to increase bioavailability although this could not be clearly demonstrated in the pivotal study. The tablets may, therefore, be given with or without food. The parent compound and the main metabolite are rapidly distributed to most tissues. Osaterone is highly plasma protein bound, however, protein binding is reversible and unaffected by other protein bound substances and no interactions with such substances are expected. Excretion is relatively slow and mainly via faeces. Accumulation occurs with repeated doses.

Target animal tolerance has been satisfactorily investigated and the product was in general well tolerated in doses of about 3 times the recommended dose, when administered for 3 days longer than the recommended period and repeated after 3 weeks.

The major side effect in most studies was a reduction in serum cortisol and reduced responsiveness to ACTH stimulation testing. These effects could last for a number of weeks after treatment, although no related clinical signs were observed. Care should, therefore, be taken in using the product in dogs whose adrenal function might be compromised. In field studies the most commonly observed side effects were related to the progestational effects e.g. increased appetite and behaviour modifications. Some transient increases in liver enzymes were noted in dogs with a history of liver disease but no evidence of hepatopathy was observed in repeat dose or tolerance studies in healthy dogs when recommended treatment dose was used. Appropriate warnings are included in the SPC and product literature. Semen quality was reported to be adversely affected in some field reports; however analysis of findings from two other studies, including one GCP study with a follow up period of 135 days following treatment, showed no variation from normal parameters.

A number of non-GLP dose determination studies and early clinical studies have shown that the optimal dose for decreasing prostatic volume and reducing clinical signs is 0.25 – 0.5 mg/kg daily for 7 days. This has been supported by a dose confirmation study and two field studies. Since the product is to be administered in the form of whole tablets, the recommended dose is stated as a range of from 0.25 to 0.5 mg per kg/day, with the dose not to exceed 0.5 mg/kg/day.

Efficacy was demonstrated satisfactorily in one large scale multicentre GCP-compliant European field study comparing the efficacy of osaterone acetate in the final formulation with delmadinone acetate as positive control in the treatment of benign prostatic hypertrophy (BPH). A clinical response to treatment (reduction of prostate volume) was seen within 14 days, which persisted for at least 5 months after treatment. Re-evaluation and re-treatment (if necessary) is therefore recommended 5 months after initial treatment. Treatment with osaterone acetate showed a similar efficacy to delmadinone acetate, which is authorised in the EU for the treatment of BPH. The results of this study were also supported by another field study using a different formulation to the final one.

Some dogs were treated concomitantly with antibiotics, but when these were excluded from the analysis, the benefits of osaterone in treatment of uncomplicated BPH were still clear. The product can be administered concurrently with antimicrobials in cases of BPH associated with prostatitis.

5. RISK BENEFIT BALANCE

Ypozane contains the active substance osaterone acetate and is presented in four tablet strengths containing 1.875 mg, 3.75 mg, 7.5 mg and 15 mg of osaterone acetate, respectively. All four tablet strengths are compressed from the same granulation. The range of tablet strengths facilitates dosing animals over a range of bodyweights. The product is packed in composite aluminium foil blisters and is presented in cartons containing 7 tablets.

The tablets are manufactured using conventional direct compression processing technology. Batch size is 50-70 kg for the bulk powder blend. The process itself is adequately described within the dossier with appropriate in-process controls detailed. Some process validation data for pilot scale batches are provided and are considered satisfactory. Validation of full scale batches will be carried out post authorisation. Full details in relation to manufacture of the active substance, osaterone acetate, are contained within the dossier. Impurities are controlled in line with VICH Topic GL10 - Impurities in New Veterinary Drug Substances. The excipients are well characterised.

The finished product specifications include tests for active substance content and identity, related substances, average tablet mass, tablet dimensions, resistance to crushing, disintegration, dissolution and blister integrity. Friability and hardness of the tablets are in-process controls. Related substance limits are in line with VICH GL11 requirements with respect to reporting levels. Analytical methods and validation for the finished product are generally considered acceptable and in line with VICH GL 2. Batch data are in accordance with the specification and show uniformity from batch to batch. 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 at 25°C/60%RH (24 months) and 40°C/75%RH (6 months) have been presented for three pilot scale batches of product packed in the packaging proposed for marketing. The product has been demonstrated to be extremely stable and the proposed shelf life of 36 months with no specific storage precautions is supported by the data presented.

Osaterone acetate is of moderate oral toxicity and low subcutaneous toxicity. In toxicity studies (single or repeat), osaterone acetate induced numerous adverse effects including severe neurotoxicity, gastrointestinal signs and lethality in various species. There were numerous differences noted between the two sexes. However, the dose rates required for such effects are several multiples of the recommended daily dose in the dog and/or occurred after long periods of administration. At lower dose rates, osaterone acetate was relatively well tolerated.

Osaterone acetate exerts several detrimental effects on reproductive function in males and females. However, since the product is not used in female animals and clinical studies in dogs did not reveal any negative impact on semen quality (as observed in rats), the CVMP concluded that no special warning is needed. Teratogenicity studies revealed developmental lesions present at mid- and high-dose rates in rats and rabbits. However, since the product is only intended for use in male dogs, the CVMP agreed that there are no teratogenic concerns in the target species based on the pattern of use. However, a warning was included in the SPC and product literature that women of child-bearing age should avoid contact with the product or wear disposable gloves, when administering it.

The data available do not indicate any mutagenic potential for osaterone acetate. Carcinogenicity studies were conducted in both the mouse and rat. Although an increase in pancreatic endocrine tumours was noted at the highest dose tested in male mice, lower doses did not reveal any effects. Similarly, in female F344 rats, an increased incidence of mononuclear cell leukaemia (MCL) was noted at the highest dose (approx. 7 mg/kg bodyweight) only. The CVMP noted that mononuclear cell leukaemia is a common finding in chronic/carcinogenicity studies using F344 rats. Taking into account that the product will only be administered to male dogs for 7 consecutive days, at intervals of several months (as compared to the 104 week administration in female rats), the CVMP concluded that NOELs for carcinogenicity could be retained for rat and mouse; both were about 3 x above the recommended dose in the dog.

User safety risk was assessed addressing various exposure scenarios relating primarily to non-professional users. It was concluded that the risks posed, particularly for susceptible sub-groups such as children and women of childbearing age, are adequately addressed by appropriate warnings in the SPC and product literature.

An environmental risk assessment was provided. As the product is intended solely for use in companion animals, the CVMP concluded that the use of the product would not cause any environmental risk.

Osaterone is a steroid chemically related to progesterone. Both osaterone and its major metabolite are pharmacologically active with potent anti-androgen activity. Osaterone acetate also expresses some progestational and glucocorticoid effects.

Following oral administration, osaterone is rapidly and extensively absorbed and undergoes a first pass effect. Administration with food tends to increase bioavailability although this could not be clearly demonstrated. The tablets may, therefore, be given with or without food. Osaterone is highly plasma protein bound, however, protein binding is reversible and unaffected by other protein bound substances and no interactions with such substances are expected. Accumulation occurs with repeated doses. Appropriate reference to this is made in the SPC and product literature.

Target animal tolerance has been satisfactorily investigated and the product was in general well tolerated in doses of up to 1.25 mg/kg, i.e. about 3 times the recommended dose of 0.25 - 0.5 mg/kg, when administered for 3 days longer than the recommended period and repeated after 3 weeks.

The major side effect in most studies was a reduction in serum cortisol and reduced responsiveness to ACTH stimulation testing. These effects could last for a number of weeks after treatment, although no related clinical signs were observed. Care should therefore be taken in using the product in dogs whose adrenal function might be compromised. In field studies, the most commonly observed side effects were related to the progestational effects e.g. increased appetite and behaviour modifications. Some transient increases in liver enzymes were noted in dogs with a history of liver disease but no evidence of hepatopathy was observed in repeat dose or tolerance studies in healthy dogs when recommended treatment dose was used. However, reference to these is made in the SPC.

A number of non-GLP dose determination studies and early clinical studies have shown that the optimal dose for decreasing prostatic volume and reducing clinical signs is 0.25 – 0.5 mg/kg daily for 7 days. This has been supported by a dose confirmation and two field studies. Since the product is to be administered in the form of whole tablets, the recommended dose is stated as a range of 0.25 to 0.5 mg per kg/day.

Efficacy was demonstrated satisfactorily in one large scale multicentre GCP-compliant European field study comparing the efficacy of osaterone acetate in the final formulation with delmadinone acetate as positive control in the treatment of benign prostatic hypertrophy (BPH). A clinical response to treatment (reduction of prostate volume) was seen within 14 days, which persisted for at least 5 months after treatment. Re-evaluation and re-treatment (if necessary) is therefore recommended 5 months after initial treatment. Treatment with osaterone acetate showed a similar efficacy as delmadinone acetate, which is authorised in the EU for the treatment of BPH. The results of this study were also supported by another field study using a different formulation to the final one.

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