EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Withdrawal assessment report for

Paccal Vet (EMEA/V/C/002237)

International non-proprietary name (INN): Paclitaxcel

Procedure No.: EMEA/V/C/002237

CVMP Assessment report with all confidential information removed.
Withdrawal at day 204

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Introduction

An application for the granting of a community marketing authorisation for Paccal Vet was submitted to the European Medicines Agency on 31 August 2010 by Oasmia Pharmaceutical AB, a recognised SME company, in accordance with Regulation (EC) No. 726/2004. The product was eligible for the centralised procedure under Article 3.2 of Regulation (EC) No 726/2004 as the product contains a new active substance, which was not authorised in the Community on the date of entry into force of the Regulation.

Paccal Vet contains paclitaxel as active substance and is presented in single-use containers of one vial. It is indicated for the treatment of non-resectable grade II or III mast cell tumours in dogs. The route of administration is intravenous. The target species is dogs.

The application was validated on 14 September 2010 and the assessment was carried out by the CVMP in line with its normal timetable. In response to questions, supplementary information was provided by the applicant on 9 September 2011, and oral and written explanations were given by the applicant on 7 February 2012. At Day 180 of the procedure, the CVMP considered on the basis of quality, safety and efficacy data submitted, that the product was not approvable, since major objections had been identified, which precluded a recommendation for marketing authorisation. The concerns were mainly in relation to the efficacy and safety of the product.

On 2 March 2012, Oasmia Pharmaceuticals AB withdrew the application at day 204 of the procedure. In its letter notifying the Agency of the withdrawal of application, the company stated the reason for the withdrawal: CVMP considered that the data provided do not allow the Committee to conclude on a positive benefit-risk balance.

Part 1 - Administrative particulars

Detailed Description of the pharmacovigilance system (DDPS)

The applicant has provided a DDPS. Based on the information provided, it is accepted that the applicant has a pharmacovigilance system in place that will allow it to comply with its legal requirements relating to pharmacovigilance.

Manufacturing authorisations and inspection status

The manufacturing authorisation for the manufacturer of the finished product was provided.

Scientific Advice

In February 2007, the CVMP provided Scientific Advice as requested by the applicant in November 2006 for several issues in relation to the clinical development of the product, i.e. pre-clinical and clinical studies. CVMP accepted that the advice was in general followed by the applicant.

Part 2 - Quality

Drug substance

The active substance, paclitaxel, is described in a monograph of the European Pharmacopoeia (Ph. Eur.) and a Ph. Eur. Certificate of Suitability has been provided for the active substance: R0-CEP 2006-320 (paclitaxel isolated from natural source). The active substance is manufactured by the CEP holder, Idena S.p.A., Milan, Italy. Certificates of Analysis have been provided from the active substance manufacturer and from the applicant. The Ph. Eur. CEP allows a re-test period of 4 years, if stored in Type III amber glass bottles closed with polyethylene undercaps and plastic screw caps.

Drug Product

Composition and container

The proposed veterinary medicinal product contains 60 mg of paclitaxel as a freeze-dried powder for solution for infusion, with the novel excipients N-(all-trans-retinoyl)-L-cysteic acid methyl ester sodium salt or XMeNa and N-(13-cis-retinoyl)-L-cysteic acid methyl ester sodium salt or 13XMeNa, and sodium hydroxide for pH adjustment. The mixture of these two components is also referred to as "XR17". It is filled into clear Type I glass vials with butyl rubber stoppers and aluminium overseals. No diluent is supplied with the product, but the product may be reconstituted with commercially available Acetated or Lactated Ringer's Solution.

Pharmaceutical development

The formulation is based on the poor solubility of the active substance, paclitaxel. The novel excipients XMeNa and 13XMeNa were chosen on the basis of their paclitaxel solubilisation capability, of the simplicity of their large scale synthesis, their low toxicity, and their micellar stability. Initially, the product was presented in a kit containing a vehicle concentrate for the reconstitution solution, which was used in the initial stability studies, two toxicity studies and pre-clinical trials. However, this was replaced by the use of a commercially available Ringer's Acetate solution, which was used for the main part of the pre-clinical research, and subsequent studies were performed to demonstrate the suitability of Ringer's Lactate solution also. The active substance is sensitive to heat and so cannot be sterilised by moist heat. It also cannot be sterilised by a validated lower irradiation dose as it is sensitive to radicals that may be produced during irradiation. Therefore it is aseptically filtered. , it is freeze-dried to avoid unnecessarily high temperatures. The manufacturing process has not been changed significantly from the manufacture of the initial batches except for scaling-up and a change in manufacturing site. The Type I glass vials were chosen for their high hydrolytic resistance, suitability for the freeze-drying process and volume for reconstitution of the product. The stopper was chosen in order to minimise product-closure interaction, for its suitability for the freeze-drying process and suitability for intended storage conditions.

Manufacture

The manufacturing process is a non-standard process involving aseptic filtration and freeze-drying. After completion of the freeze-drying process, the vials are stoppered and capped. Validation was performed on 3 consecutive production-scale batches using 3 different batches of the active substance. It indicates that a quality product in compliance with its specifications is routinely manufactured. Satisfactory justification and supporting data was provided for the overage of the novel excipients during manufacture, and for the proposed volume overage. A new procedure for

sterilising/depyrogenating the glass vials was provided, in line with the requirements of Ph. Eur. 5.1.1 "Methods of Preparation of Sterile Products". Validation data was provided for the bacterial retention and compatibility of the filters with the product and to support the proposed holding time.

Control of excipients

The excipients and sodium hydroxide are controlled in accordance with their Ph. Eur. monographs. In-house specifications have been provided for nitrogen and, and all the limits included are tighter than the requirements of their Ph. Eur. Monographs. Details of the specifications, methods and their validation for the novel excipients XMeNa and 13XMeNa are provided.

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

A declaration was provided that the only materials of human and/or animal origin used in the manufacture of the product is in the manufacture of the novel excipients, i.e. from duck and goose feathers which are exempt from the CVMP/CHMP Note for Guidance on "Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products", EMEA/410/001 Rev. 2. A declaration of the compliance of the product with the "Note for Guidance" was then provided.

Control of the drug product

Specifications have been set for appearance, identification of the active and the novel excipients, assay of the active and the novel excipients, degradation products of the active and of the novel excipients, residual solvents, reconstitution time, appearance of the reconstituted product, pH of the product reconstituted in Ringer's Acetate and Ringer's Lactate, particulate contamination for visible and sub-visible particles, water content, sterility and bacterial endotoxins.

In general, tests and limits complied with the requirements of the Ph. Eur. and/or relevant guidelines; or their absence was justified.. The methods have largely been described in sufficient detail and additional system suitability criteria was included in some of the methods. A validation for the method for detection of impurities was provided for the method for the novel excipients, but was not provided for the finished product. In general, the method validation provided demonstrates the suitability of the methods. Further detail was also provided on the accuracy and precision determinations for the validation of the HPLC methods, on the response factors in the determination of the impurities and on the ranges and linearity curves for the residual solvents GC method. Certificates of Analysis were provided for the 3 process validation batches, with all results within specification. Detail was provided on the characterisation of the impurities related to the active substance, paclitaxel, and to the novel excipients, XMeNa and 13XMeNa. Updated batch data, compliant with the revised specifications was provided. Specifications and Certificates of Analysis have been provided for the reference standards.

Stability

Stability data have been provided to 6 months for production scale batches of the finished product at the proposed storage condition of 2^{o}C – 8^{o}C and at the accelerated conditions of 25^{o}C/60% RH. All results are within specification at all times tested As all results were within specification for the 6 months data provided, a 9 month shelf-life at 2^{o}C – 8^{o}C is supported. Updated stability data was provided for these batches at 5^{o}C ± 3^{o}C/ambient RH to 12 months. All results were within the revised specifications with only minor trending apparent for total XR17 related substances. Therefore the revised shelf-life of 18 months is supported.

In addition, stability data was provided on excursion studies and for cycling between -20oC and 25oC/60% RH. The results for all three excursion studies were within specification after 7 day, 7 days and 12 days respectively, with no trending observed, which supports the removal of the requirement to transport the product refrigerated.

In-use stability data has been provided for the product reconstituted in both Ringer's Acetate and Ringer's Lactate as recommended, at 25oC/ambient RH, protected from light for 24 hours, on two batches; one fresh batch and one batch stored for 6 months. all results were within specification for both batches and for both reconstitution solutions up to 8 hours, which supports the proposed in-use shelf-life of 8 hours for the reconstituted solution. In-use stability data was provided for a batch at 19 months reconstituted in both Ringer Acetate and Ringer Lactate for functionality related characteristics such as micelle size distribution, polydispersity index, z-average size and viscosity, with very little variation seen over the 24 hours studied. In-use data was also provided for this batch for assay and degradation products of the active substance and excipients, colour, pH and visible particulates, with all results within specification for all parameters for the 24 hours studied, with increasing trends noted for the degradation products of the novel excipients. Therefore, the proposed in-use shelf-life of 8 hours is considered to be supported.

The photostability study supported the use of the storage condition "Keep the vial in the outer carton in order to protect from light".

Novel Excipients

Novel excipients, XMeNa and 13XMeNa, are used in the formulation for the solubilisation of the active substance, paclitaxel. The mixture of these two excipients is also referred to as "XR17".
Detail has been provided on their nomenclature, structure and characteristics. They are manufactured by the applicant and finished product manufacturer, Oasmia Pharmaceuticals AB Detail has been provided on the control of the starting materials and in-process controls used in their manufacture. An additional manufacturer of the starting material was subsequently added, with the same synthetic process as the original manufacturer, Oasmia Pharmaceuticals, with only minor changes to the solvents. The elucidation of their structures and characterisation of their impurities was provided, but there was an issue with respect to residual solvents. Data was provided on non-consecutive batches of the novel excipients ; however, revised specifications have not yet been provided The specifications used to control these excipients were provided, along with the test methods and necessary validation. In general the proposed specifications appear to be acceptable In addition, functionality related characteristics were requested to be included in the specifications for the novel excipients. However, acceptable justification was provided for their lack, stating that the physical characteristics of the novel excipients would be expected to be very different in the stock solution solvent, than they would be in the finished product after reconstitution. In addition, the specifications have been amended to include additional tests and the limits for some of the impurities have been tightened. Batch analysis data has been provided to demonstrate compliance with the revised specifications. Stock solutions of the novel excipients are stored in amber Type I glass bottles with a pouring ring of ethylene tetrafluoroethylene (ETFE) and a polybutylene terephthalate (PBT) screw cap with a polytetrafluoroethylene (PTFE) coated silicon seal. The specifications of the glass bottle were amended to include Ph. Eur. 3.2.9 compliant tests A and B for hydrolytic resistance for Type I glass containers. No stability data has been provided to support a re-test period for the stock solutions and so the stock solutions must be tested immediately prior to use.

Overall conclusions on quality

The dossier provides suitable detail on the active substance and the chosen formulation, with the data relating to the active substance provided in the form of a Ph. Eur. CEP, and a copy of the most recent version of the Ph. Eur. CEP was provided. Overall, the dossier seems to demonstrate that the production of the active substance and the finished product lead to consistent quality, and the issues to be addressed with respect to the batch formula, manufacturing process, in-process controls and process validation for the finished product were satisfactorily addressed.

In general, the specifications provided for the excipients and components used in the manufacture of the finished product, including the novel excipients, are acceptable. Suitable detail has been provided on the novel excipients with respect to their manufacture, characterisation and control. The finished product specification provides an assurance of the quality of the product and the tests comply with the requirements of the Ph. Eur. for the dosage form, with all issues resolved.

In general the analytical methods are well described and their suitability is confirmed by validation, and the issues on the ranges validated have been satisfactorily addressed. The method for detection of synthetic impurities, has been validated for the novel excipients. The issues on the justification of the proposed specifications have been properly addressed with respect to the tests for sub-visible and visible particles. The container closure system chosen is suitable for the dosage form and the product, however, a minor issue with respect to the specifications for the rubber stoppers still needs to be addressed.

The updated Ph. Eur. CEP allows a re-test period of 5 years, if stored in Type III amber glass bottles closed with polyethylene undercaps and plastic screw caps. Stability studies on the finished product have been performed in accordance with VICH guidelines, with the primary stability studies on-going. The proposed shelf-life of 18 months for the finished product, when stored at 2ºC to 8ºC with the vial in the outer carton in order to protect from light, is supported by the stability data provided. Additional stability data provided support the removal of the storage precaution for transporting the product refrigerated.

The proposed in-use shelf-life of 8 hours, stored at not more than 25ºC and protected from light, for the reconstituted solution has also been supported by the stability data provided, and the outstanding issues with respect to functionality related characteristics of the reconstituted solution have been satisfactorily addressed with stability data for a batch at end-of-shelf-life. The applicant also provided stability data to support the shelf-life of the paclitaxel stock solution and the in-house reference standard.

Two minor quality issueswere not satisfactrorily addressed during the procedure and remain outstanding, i.e.: minor issues with respect to the specifications for the rubber stoppers and the novel excipients.

Part 3 – Safety

Safety documentation

Introduction:

Paclitaxel is an established cytotoxic agent, which has been available for a number of years for use in humans in the management of solid tumours. The original human paclitaxel-containing product(s) was formulated with the excipient Cremophor EL (polyoxyl castor oil). Several toxic effects associated with the human product(s) were attributed to Cremophor EL. Paccal Vet is a cremophor-free formulation of paclitaxel, using two novel excipients, to increase the solubility of paclitaxel. The active substance, paclitaxel, has been extensively utilised in the treatment of cancer in humans, however the current formulation proposed for use in canine mast cell tumours is a novel formulation of paclitaxel.

Pharmacodynamics

Paclitaxel is a potent cytotoxic agent, derived from the Pacific Yew Tree (Taxus brevifolia), a member of the class of compounds known as taxanes. Its mode of action is related to the fact that it promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. The formation of stable, non-functional microtubules results in the inhibition of the normal dynamic reorganisation of the microtubule network that is essential for vital interphase and mitotic cellular functions. Cells undergoing mitosis are blocked in the late G2 phase of the cell cycle, inhibiting cell replication. Paclitaxel has also been implicated in the induction of apoptosis.

The target cells for this compound are localised to sites with actively replicating cells, including not only proliferating cells in the tumour mass but also the bone marrow, intestinal tract and hair follicles. The anti-neoplastic activity of paclitaxel has been demonstrated against a wide variety of tumour types, *in vitro* and *in vivo*, e.g. bladder, brain, breast, cervix, colon, ovary, lung, leukaemia.

The applicant provided *in vitro* and *in vivo* data confirming that Paccal Vet has a pharmacodynamic profile that is similar to a comparable human product. *In vitro* cytotoxicity of Paccal Vet was demonstrated in a panel of ten human tumour cell lines. In rats, the effect on white blood cell (WBC) counts following administration of Paccal Vet was similar to a medicine authorised for human use (in terms of the percentage decrease from baseline, nadir, duration of decrease, and stabilisation to baseline levels). It is accepted that the pharmacodynamics of paclitaxel are known due to its extensive use as an anticancer agent in humans. Based on the data presented, it can be accepted that paclitaxel, when formulated as Paccal Vet, exerts similar effects as the human medicine.

Data presented in the target animal tolerance study (Part 4.B) and the profile of adverse events observed in the clinical studies in Part 4 confirm the cytotoxic properties of Paccal Vet. Toxic effects in the target species such as myelosuppression, gastrointestinal system disorders, alopecia and abnormalities of skin (amongst others), indicate that Paccal Vet is a compound which exerts a cytotoxic effect on cells with a high mitotic index. The new excipient, XR17, showed no cytotoxic activity up to 200 µg/ml (the highest concentration tested). It is accepted that the pharmacodynamics of the active/product have been adequately characterised.

Pharmacokinetics

In support of the present application, the applicant provided reports of proprietary studies investigating pharmacokinetics of paclitaxel in the rat and the dog. In addition, the applicant provides bibliographic

data detailing aspects of the pharmacokinetics of paclitaxel in various animal species including the rat, dog and human. Based on these data, it can be concluded that:

- In the dog, protein binding is high (93-95%), similar to that reported in man.
- Paclitaxel is rapidly cleared from the circulation and is reported to have a large volume of distribution.
- In the rat, the elimination half-life is reported to be 6 to 18 h, but shorter values (2.5 h) have also been obtained. In dogs, the elimination half-life is reported to be in the range 1.9 – 6.8.
- Paclitaxel and metabolites are widely distributed into body tissues. High concentrations are initially found in the intestinal wall, adrenal, liver, kidney and lung but there is limited penetration into the brain.
- Paclitaxel is principally eliminated by hepatic metabolism and biliary excretion.
- Paclitaxel is a P-glycoprotein (P-gp) substrate. Some dog breeds (e.g. herding breeds including collies, shelties and Australian shepherds) may be at increased risk of paclitaxel-induced adverse events due to impaired P-gp activity. There is also a potential for drug-drug interactions with P-gp inhibitors.
- The available information on the metabolism shows differences between humans and rats where the former primarily form the 6-alpha-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel whereas the latter form the 3'-p-hydroxypaclitaxel. These metabolites are reported to be pharmacologically inactive. Six-alpha-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel are catalyzed by the cytochrome-P450 isozymes CYP2C8 and CYP3A4, respectively. In the dog, the metabolic profile of paclitaxel in plasma, urine and faeces when administered by intravenous infusion at a paclitaxel dose of 150 mg/m^2 was investigated. The observations made in this metabolic profiling study showing the presence of multiple hydroxylated metabolites including the 6-alpha-hydroxypaclitaxel and 3'-p-hydroxypaclitaxel in all three matrices (dog plasma, urine and faeces) are relatively similar to the metabolism data on paclitaxel reported in rats and humans.
- The results of the analyses of paclitaxel in the saliva showed that the amount of administered compound excreted through this route is very low. Similar to what has been reported in other species, faecal concentrations of paclitaxel were considerably higher (e.g. more than 30-fold 72 hours post dosing) than those in urine. The applicant calculated that approximately 95% or more of the total dose excreted in urine during the 10 days after treatment was excreted during the first 72 hours, and >64, 90 and 94% of the total dose excreted in faeces during the 10 days after treatment was excreted during the first 72, 96 and 120 hours, respectively. The concentrations in faeces at the 96 hour collection period ranged from 170 to 1380 ng/g. Based on the metabolism data generated in the dog, paclitaxel was the most significant moiety present in feces and urine.

The following text, based on the findings of the study report "Evaluation of the pharmacokinetics of paclitaxel after administration of a single dose of Paclical in dogs", was included in Section 5.2 of the SPC:

> *In dogs receiving 100-175 mg/m^2 paclitaxel as a 30 min infusion the pharmacokinetic data were found to be well described by a 2-compartment disposition model. After the infusion, there is rapid distribution of paclitaxel into the tissues, as indicated by the rapid distribution half life, in the order of 10 minutes. The distribution phase can be considered to be complete within one hour after the start of the infusion. Drug distribution into tissues was extensive according to the large Vss with a mean of 57 L/m^2. The elimination half life in the dog varied from 1.9 to 6.8 hours (median 3.0 hours). Clearance varied from 10.5 to 32.6 L/h/m^2 (median 16.6 L/h/m^2).*

Data on the plasma disposition of XR17 isomers are available from the single and repeat dose toxicity in the dog. The plasma clearance was relatively rapid with estimated elimination half-lives of the two isomers in the region of 1-3 hours recorded at 10 and 15 times the clinical dose of XR17. Information on the tissue distribution, metabolism and excretion in the rat with radio-labelled compound revealed that total radioactivity concentrated in the liver, stomach wall and, to a lesser extent, in the kidney. In the rat, more than 70% of the given radioactivity was recovered in the faeces within 120 hours after administration. Only a very low amount of the dose was found in urine. In faeces the main part of the dose was excreted as demethylated XMeNa and 13XMeNa whereas only very polar metabolites were found in the urine. Overall, the disposition data on XR17 isomers raises no safety concern.

Toxicological studies

Single dose toxicity

All acute toxicity data presented relate to the intravenous route of administration only.

The toxicity of Paccal Vet has been investigated in rats after intravenous and intraperitoneal administration. The minimum lethal dose after intravenous dosing was above 5.5 mg/kg and after intraperitoneal dosing >18 mg/kg. Effects on the liver were observed in studies with intraperitoneal but not after intravenous administration. Single dose intravenous studies with a human product, Taxol, in rats indicated that doses from 38 mg/kg (the lowest dose investigated) reduced erythrocyte and white blood cell counts and caused atrophy of the seminiferous tubules. Higher doses (85 mg/kg) were associated with deaths and thymus atrophy, bone marrow hypoplasia and lymphoid depletion of the spleen. There were also indications of local effects with gangrenous tails in an iv sighting study and adhesions and peritonitis in the intraperitoneal study.

The single dose toxicity of the novel excipient, XR17, has also been investigated after intraperitoneal administration. The minimal lethal dose was above 100 mg/kg (the only dose investigated); at this dose level there was low activity, lower body weight gain and liver findings. In the study with intravenous dosing of Paccal Vet, the dose of XR17 was 20 mg/kg. Since no toxicity was observed in this study, it is concluded that the minimal toxic dose of XR17 after intravenous dosing is >20 mg/kg.

Repeat dose toxicity

Overall, repeat dose toxicity studies conducted with Paccal Vet in rats have shown a toxicity profile similar to that of Taxol. Treatment related effects include haematological toxicity, bone marrow hypoplasia, atrophy of the thymus, and testicular and epididymal atrophy. No NOAEL could be established in the studies, while the LOAEL was 5 mg/kg bodyweight in both studies. Literature data for paclitaxel in a different formulation showed similar effects with NOAEL values of 1 mg/kg in studies for 1 month and 6 months in rats.

The intravenous route was the only route of exposure for which repeat dose toxicity was evaluated. It is argued that this is the most relevant route for assessment of the most severe user exposure situation (accidental injection).

In dogs, a repeat dose toxicity study with XR17 (infusion once every three weeks for 12 weeks) showed that high intravenous doses produce haemolysis, hepatotoxicity (which is preceded by elevated liver enzymes) and slight changes in the ECG pattern. No other organs were targeted. These results are consistent with the tissue distribution data obtained in the rat, where XR17-related radioactivity was mostly distributed to excretory organs and mainly the liver. The haemolysis and liver findings are most likely a consequence of the surfactant nature of XR17 which causes rupture of cell membranes in contact with high concentrations. The low dose (75 mg/kg) used in the dog study is considered close to

the NOAEL since there was no clinical symptoms, organ weight changes or organ damage identified. The recovery of the tissue damage observed at the high dose was not studied, but given the nature of the hepatocyte lesions and the documented full recovery of liver enzyme elevations, the tissue damage is also most likely reversible. It is considered that the effects of XR17 observed at 10 or 15 times the clinical dose will have no impact on the clinical safety in the target animal. An "overdose" at 10-15 times the highest recommended clinical dose will in all cases be fatal due to paclitaxel toxicity.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

No studies were provided for Paccal Vet. The lack of studies is justified by the knowledge about the effects on reproduction from other formulations and literature data. In a classical segment I fertility and general reproduction study, paclitaxel showed no effect on the mating index but decreased fertility occurred at 1.0 mg/kg/day. Additional effects at this dose in females were decreased adrenal, uterine, and ovarian weights as well as decreased corpora lutea, implantations and live litter sizes and increased resorptions. The NOEL in both males and females was 0.3 mg/kg.

In a classical segment II study in rats, paclitaxel showed no treatment related effects on either dams or the F1 generation except for a delay in the presence of body hair on the pups. However, the highest dose tested was only 0.6 mg/kg and it is expected that other effects would have been induced if higher dose levels were used. In similar studies in laboratory animals (study data not presented in the current application), paclitaxel administration was associated with increased resorptions and post-implantation losses, reduced birth weight, retarded ossification and skeletal malformations; the NOEL for developmental effects was also in this case determined to 0.3 mg/kg/day.

There are no data on the excipients. Regarding the excipient XR17, it is argued that reproductive toxicity studies including developmental toxicity studies would not be required for the use of this novel excipient in a non-food producing target species not intended for breeding.

Mutagenicity / genotoxicity

There have been no studies performed for Paccal Vet, justified by the extensive knowledge of the genotoxic potential of paclitaxel. Paclitaxel has shown no mutagenic activity in established *in vitro* tests but has induced chromosomal damage in both *in vitro* and in *in vivo* animal studies.

XR17 did not have mutagenic activity in the Ames Salmonella assay up to the maximally recommended test concentration of 5000 µg/plate when precautions were taken to avoid contact of the lyophilized material with normal air and other light than amber during the preparation of the XR17 solution. No other studies of mutagenic or genotoxic potential of XR17 were conducted. In accordance with current requirements *'a standard battery of in vitro and in vivo genotoxicity tests in accordance with established guidance shall usually be carried out on the active substance(s)*'. The absence of additional data is considered a deficiency in the safety data package for what is a novel excipient. However, it is accepted that the pharmacologically active substance in Paccal vet, paclitaxel, produces chromosomal aberrations *in vitro* and *in vivo* and this will be taken into account in the User Safety Assessment.

Carcinogenicity

Carcinogenicity data have not been provided.

The anti-mitotic activity of paclitaxel carries with it a mechanistically related ability to disturb the integrity of the genome. This implies a potential to induce cancer. However, the applicant notes that a study with weekly doses of 3.3 mg/kg to rats for 6 months did not result in any tumours and concludes from this that paclitaxel is not a potent carcinogen. Further, the applicant states that this conclusion is supported by the absence of literature reports clearly linking use of paclitaxel in man to the development of secondary tumours. However, it is considered that the 6 months study is too short to give definitive evidence on the lack of carcinogenic potential.

Given the nature of the active substance, further information on the carcinogenic potential will not be requested.

The carcinogenicity of the novel excipient XR17 has not been studied. This was accepted on the basis of the absence of mutagenic activity in the Ames test, the fact that no structural alerts have been identified and, when presented in the formulation Paccal Vet, the potential for long-term repeated exposure to professionals and animal owners will be very limited.

Studies of other effects

Local effects

The applicant has indicated that paclitaxel is identified as slightly skin irritant, slightly irritant to the eye and slightly irritant upon inhalation when formulated with Cremophor EL. Further, data from toxicity studies with a paclitaxel/XR17 formulation in the rat and the dog indicate that if accidental self-injection occurs irritation at the injection site is likely to be experienced. However, no specific studies have been conducted to investigate the potential for the final formulation to cause dermal/ocular irritation or sensitisation. The absence of such data is taken into account in the user safety assessment.

Observations in humans

Paclitaxel has been used in different formulations in humans for treatment of cancer. The effects and side effects are well known. A dose escalating phase I/II study, with the objectives of defining the maximum tolerable dose (MTD) and characterising the pharmacokinetics of paclitaxel (and XR17) in man, was provided. Patients that were included were those with recurrent malignant solid tumors (n=34). Patients received escalating doses (90 to 275 mg/m²) according to stepwise dose escalation scheme, until the MTD was reached.

Adverse events were reported by all human patients enrolled in the study. Overall, the most common adverse events occurring in the study were fatigue (23 patients, 68%), alopecia (18 patients; 53%), peripheral sensory neuropathy (15 patients; 44%), nausea (14 patients; 41%) and pyrexia (13 patients; 38%). Constipation and stomatitis were also relatively common, occurring in almost 30% of patients. Dose limiting toxicity was observed in 50% of the patients at a dose of 275 mg/m^2 whereas this was seen in 30% of patients at a dose of 250 mg/m^2 suggesting that the MTD in patients is in the region 200 to 250 mg/m^2. Fatigue and neuropathy were the most frequently occurring dose limiting toxicities (4 patients, 12%). Dose-limiting neutropenia occurred in 3 patients (9%) and leukopenia and stomatitis in 2 patients (6%).

User safety

A detailed user safety assessment was provided.

Paccal Vet is used for intravenous administration to companion animals. This parental route of exposure for humans should only be relevant in case of accidents (self-injection). Theoretically, other relevant routes of exposures are dermal and ocular.

In general, the likelihood of exposure is low during pre-application, application and post-application phases. For professionals, the route of exposure of most concern is accidental self-injection. For non-professional users, the most likely route of exposure to metabolized or unchanged paclitaxel/XR17 will be through indirect dermal contact via faeces, urine or other excreta.

Studies to investigate skin and eye irritation and skin sensitization have not been performed with Paccal Vet or XR17. The absence of such studies is a clear deficiency in the safety data set. However, it may be considered justified given that the potential for direct exposure is expected to be low because the product will be in the hands of professional users that will apply standard safety precautions to minimize exposure when handling such chemotherapeutic agents. In relation to systemic toxicity, the active substance has been shown to cause chromosomal damage and is identified as a potential teratogen. Based on information available from the acute and repeat dose toxicity studies, it is evident that XR17 has the potential to cause irritation at the site of injection; however, in terms of systemic effects it appears well tolerated relative to the active substance. Consequently, the focus of the user safety assessment has been on paclitaxel rather than XR17.

Potential exposure arising from direct contact in the pre-application or application phases has not been conducted, and no attempt has been made to quantify the risk associated with direct exposure. This can be accepted because it is clear that there will be no safety margin in the event of direct exposure to the active substance. That said, it is accepted that the potential for direct exposure is expected to be low because the product will be in the hands of professional users that will apply standard safety precautions to minimize exposure when handling such chemotherapeutic agents.

The amount of paclitaxel to which a professional/non-professional user may potentially be indirectly exposed has been calculated for dermal contact with faeces. Based on available excretion data for the dog, the amount of administered compound excreted through saliva is very low, such that exposure through this route is not considered to represent a risk. Similar to what has been reported in other species, faecal concentrations of paclitaxel were considerably higher (e.g. more than 30-fold 72 hours post dosing) than those in urine. The applicant calculated that approximately 95% or more of the total dose excreted in urine during the 10 days after treatment was excreted during the first 72 hours, and >64, 90 and 94% of the total dose excreted in faeces during the 10 days after treatment was excreted during the first 72, 96 and 120 hours, respectively. The concentrations in faeces at the 96 hour collection period ranged from 170 to 1380 ng/g. Based on the metabolism data generated in the dog, paclitaxel was the most significant moiety present in faeces and urine.

Using the highest concentration detected for an individual sample at the 96 hour time point, the applicant calculated potential child (10 kg) exposure to paclitaxel in faeces. The value used was 1380 ng/g faeces and it was assumed that the child would be exposed to 20 grams of the faeces and that all paclitaxel in faeces is bioavailable. In this scenario, exposure would amount to 28 µg which corresponds to 2.8 µg/kg body weight. The applicant argues that, in terms of genotoxic potential, the estimated exposure to a 10-year old child is within the limits (< 120 µg for a single exposure and < 60 µg for less than 30 days) considered safe for short term exposure for genotoxic impurities in pharmaceutical drug substances (CHMP 2010, Q&A on the 'Guideline on the limits of genotoxic impurities'). Even though the "Treshold of toxicological concern" (TTC) concept is developed for

genotoxic impurities (substances that can not be avoided) and in products for humans with a benefit for the patient to be weighed against the risk, this approach is accepted to give an idea of an acceptable level. However, as Paccal Vet is intended to be administered for 4 cycles 3 weeks apart there is a possibility for exposure for 12 weeks, even though probably not constantly. This assumption would mean that an acceptable exposure should be below 20 µg. This is true after 5 days using the worst case scenario.

A comprehensive set of user safety statements have been proposed:

- Given that the active substance has been shown to cause chromosomal damage and is identified as a potential teratogen, pregnant and breast feeding women are advised not to prepare/administer the product**.**
- The proposed SPC includes clear recommendations on the steps to be taken to minimise exposure during product preparation/administration, including recommendations to wear gloves, goggles and protective clothing.
- Contact with the urine or faeces up to 5 days after drug administration should be avoided (and not 72 hours as originally proposed). Any risks associated with indirect contact can be mitigated by wearing gloves and washing hands following potential exposure to excreta. An inadvertent indirect exposure over a more prolonged period could theoretically occur in the veterinary clinic where Paccal Vet may be used more regularly. However, again, the identified risks can be mitigated by wearing gloves and washing hands following potential exposure to excreta.

For professional users, the risk identified can be handled by safety measures in the SPC. The proposed user safety warnings for professionals are considered to be adequate. For non-professionals it can not be assumed that they will adhere to user safety warnings and use protective equipment to the same extent. It may also be difficult to keep children away from the dogs for as long as five days.

Environmental risk assessment

A Phase I environmental risk assessment was conducted. It is noted that Paccal Vet is for companion animal use only and for the treatment of an uncommon/rare disease. The only relevant exposure route will be through excretion of urine and faeces. Based on available PK data, the principal route of excretion is via faeces. It is noted that as a user safety precaution, there is a recommendation that faeces from paclitaxel treated dogs are to be collected and safely disposed of for a period of at least five days following product administration.

Based on the assessment conducted, it is accepted that there is limited potential for environmental exposure and that the risk to the environment can be considered acceptable.

Overall conclusions on the safety documentation

The pharmacodynamics and pharmacokinetics of paclitaxel have been adequately described. Paclitaxel is a cytotoxic agent from the class of taxanes, which interferes with the normal breakdown of microtubules during cell division, resulting in an inhibition of cell replication. Paclitaxel is rapidly distributed into tissues, and mainly eliminated via the faeces. Some dog breeds may be at increased risk of paclitaxel-induced adverse events due to impaired P-gp activity.

With regard to general toxicity, paclitaxel is a cytotoxic drug that in humans preferentially targets the bone marrow, cells with rapid turnover (mucosal lining of gastrointestinal tract) and peripheral nerves. In animals, lymphoid organs and the reproductive organs are also affected. Paclitaxel has shown no mutagenic activity in established *in vitro* tests but has induced chromosomal damage in both *in vitro* and in *in vivo* animal studies. No studies, with the specific purpose of investigating carcinogenicity,

have been performed. However, the applicant states that in a 6-month study repeated doses of paclitaxel caused significant bone marrow toxicity, but showed no evidence of any carcinogenicity or precancerous lesions. Still, a carcinogenic potential cannot be excluded. Paclitaxel has induced embryo-foetal toxicity including malformation in standard segment II studies in rats and rabbits. The lowest NOEL for embryo-foetal toxicity has been determined to 0.3 mg/kg. Paclitaxel is a possible human teratogen.

A detailed user safety assessment was provided. Given the nature of the active substance, in particular its potential for genotoxic and teratogenic effects, use of the product is not without risk to either the professional user (direct or indirect exposure) or animal owner/family (indirect exposure). Therefore, a comprehensive set of user safety statements have been proposed. For professional users, the risk identified can be handled by safety measures in the SPC. The proposed user safety warnings for professionals are considered to be adequate. For non-professionals it can not be assumed that they will adhere to user safety warnings and use protective equipment to the same extent. It may also be hard to keep children away from the dogs for as long as five days. These concerns will be taken into account in the overall benefit risk assessment.

It is accepted that there is limited potential for environmental exposure and that the risk to the environment can be considered acceptable, considering also the SPC instructions for collecting and safely depositing faeces from treated dogs for 5 days.

XR17 is a mixture of two novel excipients (XMeNa and 13XMeNa) and, in accordance with Title 1, Part 3 Safety and Residue tests, Chapter 1 of Directive 2009/9/EC, 'An excipient used in the pharmaceutical field for the first time shall be treated like an active substance.' This is to be interpreted as meaning that a full battery of safety tests should be provided. However, CVMP considered that in this specific formulation which consists of the excipient in a combination with the cytotoxic compound paclitaxel, the presentation of a less extensive preclinical documentation might be justified. The applicant argues that the data presented are sufficient for a novel excipient that is not expected to contribute to the toxicity profile of this specific product, is not intended for use in food producing target species, is to be used for treatment by professionals of a rare disease in companion animals only, and where exposure of the animal's owner, family and in-door and out-door environment is not considered substantial. In the context of this specific product, the absence of reproductive toxicity data, a standard battery of genotoxicity data, carcinogenicity data and local effects data has been justified. While it is accepted that the data provided are adequate to characterise the safety profile of the novel excipient XR17 when used in this specific formulation with paclitaxel dominating the safety assessment, the deficiencies in the dataset may need to be addressed should this excipient be used in the future in other unrelated products/formulations.

Residues documentation

Not applicable.

Part 4 – Efficacy

Pharmacodynamics

See Part 3.

Pharmacokinetics

See Part 3.

Dose determination / justification

The clinical dose was determined during the 'dose escalation' study. This was a single-arm, pilot study designed to investigate the safety of Paccal Vet when used for the treatment of solid tumours in the dog, with a view to determining the maximum tolerated dose (MTD).

The CVMP guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMEA/CVMP/28510/2008) specifies that the methodology and scheme used for dose escalation should be described. However, the applicant did not use a conventional approach for determining the MTD in that standard dosing cohorts and escalation/de-escalation methods were not followed. Indeed neither the initial starting dose of 175 mg/m^2, the subsequent deceleration to 100 mg/m^2, nor the method of dose acceleration and dose-cohort size were explained or justified in accordance with standard accepted dose-finding methodologies. Nevertheless, while the study to determine the MTD was not conducted strictly in accordance with current guidance, the proposed starting dose (150 mg/m^2) may be acceptable on basis of results from the dose finding study (demonstrating that a higher dose is clearly not tolerable) and the clinical field study (suggesting that a lower dose would not be sufficient from an efficacy point of view). It should be noted however that the suggested dose may be regarded as exceeding the MTD to some extent as evident by the following findings:

- Adverse effects, a substantial proportion of which are classed as severe and required supportive medication, were common in the target animal safety study when the product was administered at the recommended treatment dose,
- In the two subsequent clinical field studies, dogs were commonly subjected to dose reductions (and to a lesser extent dose delays) and to co-medication to control adverse events during the treatment cycles as a result of dose-limiting toxicity.

In terms of efficacy data presented from the dose-finding study, the applicant considered it very encouraging that, taken together, over 80% of the dogs in the PP population showed either partial or complete response to treatment; however, only very limited conclusions can be drawn regarding the effect of Paccal Vet against mast cell tumours. Only eight dogs with mastocytoma were included in the study, and no analysis of any description was performed regarding efficacy parameters for this subset of patients only. Further, the response was evaluated as the tumour response at the end of the study (9 – 10 weeks following initiation of treatment) compared to baseline. As such, the response cannot be considered as a confirmed response since the best response observed was not evaluated at a subsequent time point, e.g. 4 weeks after observation of response.

During this study, 150 mg/m^2 was chosen as the recommended dose, with the provision for dose reductions or delays for subsequent treatment cycles in the event of dose limiting toxicities (dose reduction of 10 mg/m^2 is recommended). Although the dose was associated with serious adverse events, these events were considered to be manageable with symptomatic therapy and had resolved before each subsequent cycle.

In response to a request to justify dosing on basis of body surface area it was noted that small animals will be given a much higher dose than larger dogs. While there is the potential for overdosage in small dogs, it is acknowledged that the dose will be reduced/delayed in the event of severe adverse reactions following the initial treatment cycle.

Target animal tolerance

Comprehensive data concerning the safety of Paccal Vet in the target species have been presented. This includes a target animal safety study in healthy dogs and safety evaluation in three clinical field studies. The types of adverse reactions that occurred are consistent with expectations for a non-targeted cytotoxic agent: effects are primarily limited to rapidly dividing tissue compartments including the bone marrow, gastrointestinal tract and hair follicles. The clinical manifestations of these effects are primarily neutropenia, vomiting, diarrhoea, anorexia, depression, lethargy, pyrexia and alopecia.

A large proportion of treated dogs experienced neutropenia, and in many cases severity was graded as 3 or 4 according to the Veterinary Co-operative Oncology Group criteria (i.e. "severe" or "life-threatening"). For a substantial proportion of treated animals, the severity of the adverse effects, especially at the first cycle of treatment, necessitated supportive care (including intravenous fluids, antimicrobials and/or anti-emetics).

Tolerance appears to improve to a degree following the second and subsequent treatment cycles, although 'severe/life-threatening' neutropenia occurs approximately 4 – 7 days after each cycle. Typically, side-effects resolved within two weeks and dogs were fit for the following cycle; however, doses were commonly reduced by at least one incremental step during the treatment cycles in each of the clinical field studies.

The effects of an overdose or increased duration/frequency of dosing were not investigated in the target animal safety study. However, based on available data, it is clear that there is no margin of safety for this product. In line with the CVMP guideline on dossier requirements for anticancer medicinal products for dogs and cats (EMEA/CVMP/28510/2008), and the scientific advice given to the applicant prior to submission of the dossier, the margin of safety concept is not relevant for cytotoxic compounds given that toxicity is dose-limiting, thus overdose studies in the target species are not required.

Although adverse reactions are to be expected for a cytotoxic compound, it is reasonable to question if the severity of the adverse reactions encountered following administration of paclitaxel are acceptable.

Finally, based on available data, it would appear the excipient XR17 does not contribute to the toxicity of the product.

Field trials

The clinical efficacy and safety of Paccal Vet has been investigated in one GCP dose-escalation study (commented on above), one GCP open-label clinical study, and in one confirmatory GCP clinical field study.

GCP open-label clinical study

This was a GCP compliant, multi-centre open single arm study with the objective of determining efficacy and safety of the product for the treatment of mast cell tumours in the dog. The study was conducted at sites in Sweden, Germany and Austria. Client-owned dogs received at least one cycle of treatment. The test product, Paccal Vet, was administered as an intravenous infusion every three weeks for three cycles at a dose of 150 mg/m^2. After one completed dose, a dose adjustment

(reduction or delay) was allowed based on dog tolerance. Safety and efficacy measurements were carried out on day 1 (before treatment), day 4, and day 7 of each cycle, at study termination and at 6 month follow-up.

31% of dogs were withdrawn from the study due to death or euthanasia. The main cause of death was progressive disease (n=4), euthanisia at the owner's request (n=3), one dog experienced disseminated intravascular coagulation and died five days after the first treatment, and one dog suffered an acute anaphylactic reaction considered to be due to acute tumour lysis syndrome (ATLS).

Of the dogs that were protocol-compliant and received three cycles of treatment, 55.6% showed complete response or partial response as the best target lesion response observed from start of treatment until study termination (9 – 10 weeks after initiation of treatment); and 38.9% showed complete response (n=1) or partial response (n=6) according to the overall response evaluation at study termination.

While the results of this study show indications of efficacy, they must be interpreted with caution given that the study did not employ a control. Further, it is noted that several dogs were withdrawn from the study due to death or euthanasia (a number of which were due to progressive disease). Therefore, if efficacy is considered based on number of animals that received at least one treatment, then the success will be somewhat lower (this has been calculated to be 31.0%). Also, the study design did not allow for confirmation of response, thus it is possible that the study overestimated the response. In this study, there are no useful data concerning temporal measures of efficacy.

Safety measurements have confirmed findings from other studies with regard to the nature of adverse reactions. The principal adverse effects relate to effects on white blood cells: neutropenia, classified as severe and life-threatening (VCOG grades 3 and 4), was commonly observed. The nadir occurs at 4 – 7 days following treatment and resolves prior to the next cycle of treatment. Other commonly observed adverse events included gastrointestinal disturbance (vomiting, diarrhoea, anorexia), alopecia and thrombocytopenia. All dogs experienced adverse events and serious adverse events occurred in 48.3% of the dogs during the first cycle and to a somewhat lower frequency in the subsequent cycles.

GCP clinical field study

This was a randomised, blinded, controlled, clinical field study to determine the efficacy and safety of Paccal Vet (paclitaxel micellar) for treatment of non-resectable grade 2 or 3 mast cell tumours in dogs. The study was conducted in accordance with GCP at multiple sites in USA, UK, Sweden, Germany and Italy. A large number of client-owned dogs with grade II or III non-resectable mast cell tumours were included in the study. The test product, Paccal Vet, was administered as an intravenous infusion every three weeks at a dose of 150 mg/m^2. After one completed dose, a dose adjustment (reduction or delay) was allowed based on dog tolerance. Lomustine was administered as positive control. A superiority study design was employed and the choice of comparator was based on the fact that no veterinary approved positive control was available at the time the study started. The rationale for the dose used was based on published data and from consultation with veterinary oncologists. Safety and efficacy measurements were carried out on day 1 (before treatment), day 4, and day 7 of each cycle, at study termination (Day 35 of cycle 4).

Efficacy

The primary endpoint was the proportion of dogs with a response evaluation criteria in solid tumour (RECIST) score of 'complete' (CR) or 'partial' (PR) after four consecutive 21-day cycles of treatment. The primary objective was to determine the 'confirmed overall response' (ORR), defined as CR or PR at visit 13 (=cycle 4, day 7) and confirmed at visit 14 (=cycle 4, day 35). All other dogs were considered as non-responders.

The response to treatment observed in the Paccal Vet group was very low, with only 7% of animals with confirmed ORR at the end of the study. The corresponding figure for the control group (lomustine) was only 1 %. Based on the data analysis conducted, the applicant concludes that a statistically significant treatment effect in favour of Paccal Vet is demonstrated (p=0.048). However, from a review of the data, CVMP concluded that the robustness of the statistical analysis was questionable.

A post-hoc analysis of the data in the pivotal field study shows that when stable disease at 14 weeks is included in the overall response rate, 26% of dogs treated with Paccal Vet have complete response, partial response or stable disease at 14 weeks following initiation of treatment. While this analysis does show a more compelling benefit of treatment, it was not defined prior to conduct of the study, thereby lessening the value of the analysis. Furthermore, treatment effect is likely less well reflected by stable disease on short term, since tumour development may inherently pass stable periods and furthermore, for a cytotoxic substance tumour shrinkage is to be expected. While it is accepted that anti-angiogenic and anti-proliferative effects may be reported for paclitaxel, the claimed mode of action is cytotoxic.

In the current study, temporal measures of efficacy were not included in the analysis. Therefore, in addition to the modest outcome in terms of tumour response, the clinical benefit of treatment remains unclear.

Safety

Safety data in this study confirmed the toxicity profile characterised in the previous studies, with severe dose-limiting side effects such as neutropenia, vomiting, diarrhoea, anorexia, lethargy, dehydration, pyrexia and alopecia observed in treated dogs. Among Paccal Vet treated animals almost all dogs (99%) experienced adverse events or reactions and the most common events where neutropenia (82%), emesis (79%), anorexia (76%), diarrhoea (70%), lethargy (59%), alopecia (39%), dehydration (26%), dermatitis (24%), hepatopathy (19%) and pyrexia (13%). Among these, neutropenia (93%) and hepatopathy (49%) occurred more commonly in lomustine treated animals, but the other events were more commonly noted in Paccal Vet treated dogs. In total 83% of the Paccal Vet treated animals experienced a severe adverse event and 17% suffered a serious/life threatening event. In the Paccal Vet group, the incidence of dose modifications (a measure of dose limiting toxicity) was high (but similar to the lomustine group); the dose was reduced for 42% of dogs and was delayed for 9% of dogs. In relation to the quality of life data, the following is noted:

- On Day 4 of the first cycle, there is a difference in quality of life (as determined by the investigator) between the treatment groups with 49% of Paccal Vet dogs with scores classed as not 'normal', compared to 12% of lomustine dogs. Furthermore, this difference is even more pronounced when the owner's evaluation of performance score is considered.
- Nausea, anorexia, vomiting, and diarrhoea were generally highest on Day 4 of each cycle, and were more common in the Paccal Vet group compared to the lomustine group.

In conclusion, while a statistically significant treatment effect in favour of Paccal Vet, relative to lomustine, for the treatment of non-resectable grade II or III mast cell tumours is claimed, the response to treatment observed in the Paccal Vet group is considered very low. The low efficacy as determined by the primary efficacy criterion, together with absence of data on temporal measures of efficacy, provides only limited support for the claimed indication. Against that, the incidence of adverse effects is high and treatment has the potential to impact on Quality of Life for a substantial proportion of treated dogs.

Overall conclusion on efficacy

Of the three clinical studies investigating the efficacy of Paccal Vet, the two pilot studies yielded encouraging results. However, both studies had design flaws such that the findings must be interpreted with caution. In the pivotal field study, the response rate was much lower compared to the pilot studies, with only 7% of dogs in the Paccal Vet group determined to have a confirmed complete or partial response to treatment. In addition to the modest outcome in terms of tumour response, the clinical benefit with respect to temporal measures of efficacy such as progression free survival, overall survival or time to treatment failure were not included in the primary or secondary endpoint analysis and therefore cannot be evaluated.

Part 5 – Benefit risk assessment

Introduction

Paccal Vet contains paclitaxel and is presented in single-use containers of one vial. It is indicated for treatment of non-resectable grade II or III mast cell tumours in dogs. The route of administration is intravenous use. The target species is dogs.

While there are other authorised products for the treatment of mast cell tumour in the dog, the active substance paclitaxel is new to the veterinary field.

Benefit assessment

Direct therapeutic benefit

Paclitaxel is a potent cytotoxic agent. In man, the anti-neoplastic activity of paclitaxel has been demonstrated against a wide variety of tumour types.

Of the three clinical studies investigating the efficacy of Paccal Vet in the dog, the two pilot studies yielded encouraging results. However, both studies had design flaws such that the findings must be interpreted with caution. In the pivotal field study, the response rate was much lower compared to the pilot studies, with only 7% of dogs in the Paccal Vet group determined to have a confirmed complete or partial response to treatment.

Overall, from an efficacy point of view, the benefit demonstrated to dogs with grade II or III non-resectable mast cell tumours following treatment with Paccal Vet under the proposed conditions of use appears low.

Additional benefits

Paccal Vet exerts its effect by stabilising tubulin during mitosis and thereby preventing cell division. This mode of action is different in comparison to currently available treatment options for dogs with mast cell tumours (based on tyrosine kinase receptor inhibitors).

Risk assessment

The types of adverse reactions that occurred are consistent with expectations for a non-targeted cytotoxic agent: effects are primarily limited to rapidly dividing tissue compartments including the bone marrow, gastrointestinal tract and hair follicles. The clinical manifestations of these effects are primarily neutropenia, vomiting, diarrhoea, anorexia, depression, lethargy, pyrexia and alopecia. For a substantial proportion of treated animals, the severity of the side effects, especially at the first cycle of

treatment, necessitated supportive care (including intravenous fluids, antimicrobials and/or anti-emetics).

Treatment has the potential to impact on quality of life for a substantial proportion of treated dogs. In the pivotal field study, on Day 4 of the first cycle, there is a difference in quality of life (as determined by the investigator) between the treatment groups with 49% of Paccal Vet dogs with scores classed as not 'normal', compared to 12% of lomustine dogs. Further, nausea, anorexia, vomiting, and diarrhoea were generally highest on Day 4 of each cycle, and were more common in the Paccal Vet group compared to the lomustine group. All animals treated with Paccal Vet will be expected to demonstrate adverse reactions and many of these will be serious in nature.

Given the nature of the active substance, in particular its potential for genotoxic and teratogenic effects, use of the product is not without risk to either the professional user (direct or indirect exposure) or animal owner/family (indirect exposure). Therefore, a comprehensive set of user safety statements have been proposed.

It is accepted that there is limited potential for environmental exposure and that the risk to the environment can be considered acceptable considering also the SPC instructions for collecting and safely depositing faeces from treated dogs for 5 days.

Evaluation of the benefit risk balance

From an efficacy point of view, the benefit to dogs with grade II or III non-resectable mast cell tumours following treatment with Paccal Vet under the proposed conditions of use appears modest as only 7% of included dogs met the primary objective of the pivotal field trial (overall response rate) and the long term benefits cannot be evaluated.

The low response rate with respect to efficacy should be balanced against the fact that in clinical field studies, paclitaxel-treated dogs experienced a high incidence of adverse reactions, in particular severe neutropenia, but also several other events expected to cause discomfort/suffering, which for many dogs required medical intervention to restore the animals' clinical condition. Treatment has the potential to impact negatively on Quality of Life for a substantial proportion of treated dogs.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the Paccal Vet is not approvable at the present time, since "major objections" have been identified which preclude a recommendation for marketing authorisation.