7 March 2013
EMA/169948/2013
Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Oncept IL-2 (EMEA/V/C/002562/0000)

Common name: Feline interleukin-2 recombinant canarypox virus (vCP1338 virus)

Assessment report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Introduction

The applicant MERIAL submitted on 26 October 2011 an application for marketing authorisation to the European Medicines Agency (The Agency) for Oncept IL-2, through the centralised procedure falling within the Article 3(1) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CVMP on 5 May 2011 as Oncept IL-2 contains a new active substance which is developed by means of recombinant DNA technology.

The CVMP adopted an opinion and CVMP assessment report on 7 March 2013.

On 3 May 2013, the European Commission adopted a Commission Decision for this application.

Oncept IL-2 contains feline interleukin-2 recombinant canarypox virus (vCP1338) and is presented in packs of 6 vials of 1 dose lyophilisate and 6 vials of 1 ml of solvent. It is indicated for immunotherapy to be used in addition to surgery and radiotherapy in cats with fibrosarcoma (2-5 cm diameter) without metastasis or lymph node involvement in order to reduce the risk of relapse and to increase the time to relapse (local recurrence or metastasis). The route of administration is subcutaneous. The target species is cats.

Upon request from the applicant the Committee confirmed at their May 2011 meeting that the data requirements in the guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMEA/CVMP/IWP/123243/2006-Rev. 2) would apply. MUMS status was granted as fibrosarcomas are rare in cats.

Part 1 - Administrative particulars

The dossier does not contain any detailed or critical summaries, which is accepted in accordance with the guideline on data requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets.

The CVMP considers that the detailed description of the pharmacovigilance system as described by the applicant fulfils the requirements of Directive 2001/82/EC, and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Union or in a third country.

Oncept IL-2 is manufactured by MERIAL in France. Valid GMP certificates are available for the drug substance manufacturing site and/or the drug product manufacturing site and/or the batch release site. MERIAL sites were inspected in 2011 and judged to be in full compliance with legislation.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

Oncept IL-2 is constituted of a lyophilisate fraction containing the live active ingredient - a recombinant canarypoxvirus expressing feline interleukin-2 at a minimal dose of 10^6 EAID50 - to be reconstituted in water for injections before use.

Container

The two product fractions are filled in type I glass vials closed with a butyl elastomer stopper and sealed with an aluminium cap.

Development pharmaceutics

The active ingredient is a suspension of live feline interleukin-2 recombinant canarypox virus.

Choice of the active ingredient

Systemic delivery of interleukin as adjunct immunotherapy in cancer patients has limited applications due to severe toxicity at the dose range required to achieve clinical response. Intratumoural or peritumoural IL-2 delivery of small doses were shown to cause tumour regression at low doses and with reduced systemic toxicity in numerous experimental models. The local delivery of IL-2 can be done using specific formulation of recombinant IL-2 or by expressing IL-2 locally with cells or expression vectors. The choice of the canarypox virus as feline IL-2 vector (ALVAC) was motivated as this vector does not multiply nor disseminate in mammals, is safely used in cats in vaccines already on the market and is well-known by the applicant. Canarypoxvirus can be considered as a viral factory to deliver low amounts of IL-2 in a more prolonged way than if IL-2 would be directly injected locally. Interleukin being a cell messenger, a prolonged and low localised production increases the success of the message delivery.

The manufacturing process is a classical process of production of canarypox virus on chicken embryo fibroblasts and is similar to the one used for some existing recombinant canarypoxvirus vaccines. For formulation, the antigen is quantified based on the detection of a cytopathic effect (CPE) on chicken-embryo cells expressed in $CCID_{50}$, which is a classical method used in various existing products and is fully validated. The active ingredient is quantified by detection of the IL-2 expressed in the supernatant of infected cells by ELISA. This method has been demonstrated to be strictly correlated with CPE method and from a biological point of view, one can consider than 1 $EAID_{50}$ corresponds to 1 $CCID_{50}$. Classical containers and closure are used. The overage applied in order to ensure the stability of the product throughout the claimed stability period is justified as well as the minimal and maximal release specification to ensure safety and efficacy of the product.

The choice of the antigen concentration was adequately described and justified.

Description of stages of production

The active ingredient is a suspension of live, recombinant feline interleukin-2 canarypox virus, multiplied in SPF chicken embryo cells. A seed lot system is used for the preparation of active ingredients. Batches of active ingredient consist of the 5th passage at most in SPF chicken embryo cells, from the Master Seed Virus (MSV).

Preparation of finished product

The active ingredient is transferred into the preparation vessel. The necessary volume of freeze-drying substrate is calculated and the substrate is added slowly to PBS. The bulk obtained is maintained at 5 °C until filling.

The product is filled into sterile bottles with a filling equipment so as to guarantee 1 ml per bottle.

Secondary packaging

One dose is constituted of one bottle containing the freeze-dried pellet and one bottle of diluent. The presentations are then labelled, packaged and stored in cold room until dispatch.

All bottles coming from the same final lot and labelled during the same operation constitute a commercial lot.

The CVMP considered the method of manufacture to be correctly documented and sufficiently demonstrated as well as the consistency of the manufacturing process to be adequately demonstrated.

Control of starting materials

All the starting materials were provided with sufficient information regarding their sourcing and specifications (most in line with European Pharmacopoeia (Ph. Eur.) monographs) to justify their inclusion in the manufacturing process.

Genetic engineering techniques were used in order to generate an ALVAC-based recombinant virus (designated vCP1338) containing the feline interleukin-2 gene. ALVAC: plaque purified cloned obtained from a highly attenuated vaccine for canary birds (KANAPOX, MERIAL) derived from canarypox virus.

This vector and the derivative recombinants were shown not to replicate in tissue culture cells derived from non-avian species. A specific ALVAC construct was used to demonstrate the inability of ALVAC to replicate in mammalian cells of canine and feline origin (contrary to a vaccinia-based recombinant). A study was provided to show the vCP1338 virus did not replicate in several mammalian cell types during successive passages, whilst replication was clearly observed in primary chicken embryo cells. These results confirm observations that recombinant canarypoxviruses are replication defective in mammalian cells.

The CVMP considered that these recombinant canarypoxviruses in MERIAL veterinary vaccines have already been authorised in Europe and the above mentioned data have already been assessed. Absence of replication *in vitro* in mammalian cells has been specifically assessed and confirmed for the vCP1338 recombinant virus in the current product.

The CVMP concluded that sufficient information has been provided on the construction of the recombinant virus, including source of parental virus and donor plasmids.

The CVMP concluded that all starting materials are controlled according to applicable guidelines or pharmacopoeia. Controls performed on the starting materials of biological origin associated with validated treatments ensure quality of the materials and absence of risk of transmission of extraneous agents through the use of these materials.

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

The following raw material of bovine origin are involved in the manufacturing process: lactose monohydrate, tryptose phosphate broth, foetal calf serum, iron-supplemented calf serum, calf serum and casein hydrolysate.

The active ingredient comes from an avian virus strain and is prepared in presence of bovine raw materials with lower or no detectable infectivity.

Manufacturing process

The master seed inoculum is firstly diluted in the culture medium to amplify the seed in order to establish the working seed. Further, the working seed inoculum is diluted in the culture medium to prepare the virus suspension. Finally, the active ingredient is diluted in the excipient to blend the final product.

Intended species and route of administration

The final product is administered to cats by the subcutaneous route, which is considered an administration route of relatively low risk with regard to transmission of TSE.

The risk of transmitting TSE through the product can be considered as extremely minimized.

The CVMP concluded that the risk of transmitting TSE through Oncept IL-2 has been assessed in compliance with the current regulatory texts and can be considered as extremely low.

Control tests during production

On the active ingredient tests for bacterial and fungal sterility as well as titration for canarypoxvirus in chicken embryo cells was performed.

Validation of titration method was considered satisfactory by the CVMP. Appropriate in-process tests are performed to monitor regularity of the production and compliance with the manufacturing process namely: Sterilising filter integrity, time recording, temperature recording, monitoring of the sterilisation cycle, checking the filled volumes, monitoring of the freeze-drying cycle, appearance, conformity of presentations.

The investigation of the in-process parameters tests the conformity of the process with regards to defined requirements which is an additional guarantee of quality of the produced products.

The CVMP concluded that the tests in place are adequate to control the manufacturing process of this product and the applicant has provided data on three consecutive batches of active ingredient manufactured at production scale to show consistency of production. The results are within specifications. Appropriate in-process controls including titration of the active ingredient are investigated and guarantee consistency and homogeneity of the production as well as absence of introduction of any extraneous agents during the process.

The control tests on the finished product included visual appearance, pH, identification and titration of the active ingredient, safety testing, tests for bacteria and fungal sterility and mycoplasmic sterility as well as viral purity and residual humidity.

The CVMP concluded that the tests in place are adequate to control the finished product.

Identification of active substance(s) – batch titre potency

On each batch, this control is based on ELISA signal showing expression of IL-2 in cell culture supernatants.

Validation of this control technique on the identification and quantification of feline interleukin-2 recombinant canarypoxvirus (vCP1338) contained in Oncept IL-2 products was performed for specificity, linearity and precision.

The CVMP concluded that this is validated with regard to precision in finished product batches. Linearity has been demonstrated in the range of the specification limits set for the finished product. Data on equivalence of titration results in the 2 control sites – Lyon Gerland and lyon LPA have been provided.

Data on equivalence of this titration method with one titration method based on cytopathogenic effect of canarypoxvirus have been provided. The CVMP considered the results for the two control techniques acceptable and concluded that the 2 control methods can be considered as equivalent.

The CVMP noted that the equivalence established in this study confirms validity of all the product batches controlled with one or the other method used in the safety and efficacy studies.

Sterility and purity test

The results show that the detection of contaminant viruses in cell cultures is not hampered by the presence of vCP1338 virus.

These observations confirm that the detection of viral contaminants in finished product can be carried out without neutralisation of the vCP1338 virus.

Residual humidity

A minimum level of residual humidity has been specified, as too little moisture can be as deleterious to a freeze dried pellet as too much.

Overall the CVMP concluded that the description of the methods used for the control of the finished product (identity, purity, titre, safety, sterility, viral purity, residual humidity) and the specifications provided are satisfactory.

The results of the analysis of three consecutive production runs of freeze-dried product and for three consecutive production batches of diluent (water for injections) were presented and comply with the required specifications.

Stability

Stability data are available for 3 batches of freeze-dried fraction formulated at a lower target titre than described in part II for 21 months and 3 batches manufactured according to II.B. stored for 15 - 21 months.

The overall results validate the proposed 15 months stability at 5 +/- 3 °C protected from light.

On the data on the stability of the aqueous diluents filled in glass vial stored at 5 +/- 3 °C the CVMP concluded that all chemical and physical parameters are controlled in conformity with finished product specifications after 39 months storage.

No specific data are available on the stability of the reconstituted product because the applicant argues that the product should be administered immediately after reconstitution of the freeze-dried fraction in the diluent. This is acceptable.

Overall the CVMP concluded that the claimed stability period is 15 months at 2 - 8 °C for the lyophilisate fraction.

Overall conclusions on quality

The manufacturing process is well described and complies with the relevant regulatory requirements.

The starting materials of biological origin pose an extremely low risk with respect to the transmission of TSE and other extraneous agents. This is acceptable.

The control tests performed during production are adequately described and include sterility of the medium, purity check, test on inactivation and antigen content and sterility determination of the inactivated antigens.

The description of the methods used for the control of the finished product and the specifications are adequate. The analytical methods are considered validated and the specifications proposed at release are appropriate to control the quality of the finished product.

The IL-2 content determination is acceptable and ensures that correct amounts of the active ingredient are added to the final product.

The final product controls for Oncept IL-2 are in acceptable range for this type of product.

The stability data provided justify a shelf-life of 15 months for the final product.

Overall, the CVMP considers that the manufacturing process is described in sufficient detail to give confidence that the finished product is produced according to a consistent procedure of adequate standards and including adequate controls, to ensure that only safe and efficacious batches of vaccine are produced.

Part 3 – Safety

Oncept IL-2 is an immunological veterinary medicinal product containing a recombinant canarypoxvirus (vCP1338) expressing feline interleukin-2 (IL-2).

IL-2 is a relatively small glycoprotein (154 aminoacid protein sequence in the gene) produced by activated T lymphocytes. IL-2 is a soluble factor stimulating the proliferation of lymphoblasts *in vitro*. *In vivo*, it is involved in many different functions, participating to the regulation of the immune response. As an enhancer of the immune response, IL-2 is a promoter of B and T cell proliferation, of maturation of cytotoxic T lymphocytes and lymphokine activated killer cells, activation and proliferation of natural killer cells and immunoglobulin synthesis.

This interleukin is known for activating immune mechanisms involved in the rejection of tumours and therapeutic approaches based on local IL-2 release into the tumour or surrounding tissues have been devised to circumvent dose-limiting toxicity associated with systemic release of the interleukin.

Oncept IL-2 is intended to be used as immunotherapy to be associated with surgery and radiotherapy in order to reduce the risk of tumour recurrence and metastasis in cats with fibrosarcoma. The production of IL-2 allows the stimulation of a local immune response against tumour cells at the inoculation site.

The active ingredient being a live virus – although replication-defective in the target species - tests for live products were performed. Safety was tested both under laboratory and field conditions in cats of various age, sex and breed. Batches deliberately formulated at a high dose were used for these studies (formulation higher than those described in the quality part).

During development, the titration technique evolved from the CPE technique to an ELISA-based method detecting produced IL-2 in cell culture supernatants. This has no consequence on the relevance of the data on products and studies as strict bioequivalence between both methods has been established.

Immunostimulatory cytokines modifying local inflammatory reactions (such as interferon alpha, beta, GM-CSF IL-1,2 and IL-2) may induce tumour regression. Recombinant virus makes it possible to express genes of interest locally for a prolonged period.

Regressions of variety of tumour types, most commonly renal cell carcinoma and melanoma, have been observed after treatment by IL-2 in humans. In Europe, PROLEUKIN has been authorized for treatment of metastatic renal adenocarcinoma. In this indication, IL-2 is to be administered at high dose by intravenous route or by subcutaneous route.

Toxicity of IL-2 using high dose regimen essentially with intravenous treatment is well documented and adverse reactions involve especially:

- cardiovascular toxicity with hypotension,
- nephrotoxicity (azotemia, oliguria),
- pulmonary toxicity (pulmonary oedema caused by poor cardiac function),
- gastrointestinal toxicity (nausea, vomiting and/or diarrhoea, anorexia),
- endocrinologic and metabolic toxicity (hypothyroidism, elevation of cortisol, drop in serum cholesterol),
- dermatologic complications (macular erythema, stomatitis...),
- neurologic toxicity (agitation or somnolence, comatose),
- hematologic toxicity (anemia, transient lymphopenia, rebound lymphocytose, eosinophilia, thrombocytopenia),
- fever and chills,
- infections,
- disease exacerbation.

These adverse reactions can be directly attributed to IL-2 but also to cross-regulation and to other cytokines activated during the treatment. Recent data on interleukin-2 suggest the complex role of this cytokine at the interface between tolerance and immunity. Decreased IL-2 production is often observed in more advanced clinical stages of many tumours, which provides rationale for inclusion of recombinant IL-2 in the immunotherapy for some tumours. In other cases, tumour cells themselves may produce IL-2, which promotes tumour growth.

It is currently not fully understood which underlying mechanisms lead to a specific role of IL-2 and in which conditions IL-2 acts on effector cells differentiation and proliferation or on generation and maintenance of T Reg; in particular there is uncertainty whether this depends on the stage of the immune response, the dose of IL-2 or the kinetics of IL-2 production.

IL-2 acting on the immune response of animals may trigger unwanted effects that may be observed long time after treatment and consequences of the treatment under such conditions should be considered with particular caution. The data provided in the safety part have been examined in the light of these data.

Since the Committee confirmed that the requirements for immunological veterinary medicinal products intended for minor use or minor species/limited markets (EMEA/CVMP/IWP/123243/2006-Rev2) were applicable for this application the scientific assessment conducted on the safety part of the dossier has been carried out taking into consideration that some reductions in requirements are acceptable and this is addressed in the discussions below.

Laboratory studies

Safety of the administration of one dose, an overdose and repeated dose

Evaluation of the safety of the recombinant canarypox feline interleukin-2 (vCP1338) when administered in cats as an overdose by subcutaneous route (s.c.).

This study was performed in 12 SPF cats aged around 7 months with a product containing vCP1338 at overdose (10 doses). Group A contained 8 cats and was given 1ml of the product by the s.c. route and Group B contained 4 cats and was given 1ml of saline by the s.c. route. Monitoring was performed for local and general reactions 4 hours after injection and daily during 14 days including recording of rectal temperature, (D0, D0+4h, D1 to D4) and weighing (D0, D7, D14). Collection of blood samples was performed on D-7, D-4, D1, D4 and D14 for haematology and biochemistry analyses (urea, creatinemia, alanine aminotransferase, alkaline phosphatase and protein). Collection of rectal and pharyngeal swabs was done on D1 and D4 for canarypoxvirus detection (on CEF).

The results were presented as numeric and graphic descriptive analysis of the data. The biochemical and haematological parameters were compared to reference values.

All cats remained healthy during the observation period and there was no difference in weight gain between both groups transient moderate to marked hyperthermia up to 40.4°C was observed on D1 in 6/8 cats from group A (not associated with alteration of body condition) and an oedematous swelling was observed in 6/8 cats from D1 (≥2cm), disappearing in 2-3 days or evolving to small size nodules (<0.5 cm) still palpable on D14 (6/8 cats). Erythema lasting 2-3 days (4/8 cats), slight pain (2/8 cats) and cutaneous heat (1/8 cat) was also observed. At necropsy, slight inflammatory mononuclear cell infiltrates and severe panniculitis lesions. White blood cells counts were increased in most of the group A cats (7/8) at D1 but returned rapidly to reference values. No other significant variation of biological parameters was observed. No canarypoxvirus was isolated from the rectal and pharyngeal swabs collection at D1 and D4.

This study provides assurance on the safety of the canarypoxvirus vector. It provides additional information on safety administration of the whole 1 ml dose of Oncept-IL2 in one point injection.

The data should be considered together with the field studies for the assessment of safety of the recommended treatment and of IL-2 as the cats in the study are SPF cats not being the target population as the treatment is recommended for operated cats with inflammatory reactions and also considering that one single injection is not representative of the recommended method of administration. Moreover it seems that the injection of 1 dose of Oncept IL-2 as one injection in cats leads to a low quantity of IL-2 (without any dose-effect). The adverse effects seen in this study are therefore not included in the SPC.

Overall the CVMP concluded that this study confirms some expected properties of the canarypoxvirus i.e. absence of identified excretion in pharyngeal and rectal swabs.

Evaluation of the safety of the recombinant canarypox feline interleukin-2 (vCP1338) when administered in cats as an overdose by intravenous route.

This study was performed in 12 SPF cats aged around 7 months with a product containing vCP1338 at overdose (10 doses). Group A contained 8 cats and was given 1ml of the product by the i.v. route and Group B contained 4 cats and was given 1ml of saline by the i.v. route. Monitoring was performed for local and general reactions 4 hours after injection and daily during 14 days including recording of rectal temperature, (D0, D0+4h, D1 to D4) and weighing. (D0, D7, D14) Collection of blood samples was performed on D-7, D-4, D1, D4 and D14 for haematology and biochemistry analyses (urea,

creatinemia, alanine aminotransferase, alkaline phosphatase and protein). Collection of rectal and pharyngeal swabs was done on D1 and D4 for canarypoxvirus detection (on CEF).

The studies were presented as numeric and graphic descriptive analysis of the data including a comparison of relative daily weight gain between groups by Student t-test (5%). The biochemical and haematological parameters were compared to reference values (mean D-7, D-4).

Apathy was observed in all cats from group A 4 hours after injection and there was also diarrhoea in 1kitten at 4h but all reactions disappeared spontaneously within 1 day. There was no difference between groups for weight gain. There was however transient moderate to marked hyperthermia 4 h after injection (4/8 cats) or on D1 (1/8). No local reactions were observed except phlebitis in 1 cat which may be imputable to the injection procedure. The WBC count sometimes was decreased on D4 (6/8 cats from group A) but no clinical signs were associated with this decrease and values returned to normal on D14. There were no other significant variation of biological parameters.

No canarypoxvirus was re-isolated from the rectal and nasal swabs collected on D1 and D4.

The CVMP considered it is important to note that in a physiological context, there is no IL-2 in the blood. IL-2 is a local cytokine produced at an inflammatory site. Data demonstrate that after intravenous injection of the product, only mild side effects are to be expected; not important compared to the adverse reactions that are observed after intravenous administration of high quantity of IL-2. Overall this study can be considered as supportive, as the route of administration is different from the recommended. Nevertheless, the information provided is valuable and it supports the safety of the product when administered by the 'worst scenario' route (based on literature data).

ALVAC IL-2 (vCP1338): Safety study in conventional cats

This study was performed in 50 healthy cats aged around 14-17 months with a product containing vCP1338 at a high dose.

Administration of the product was done in accordance with the recommended protocol: 4 treatments at 1-week interval (D0, D7, D14 and D21) followed by 2 treatments at 2-weeks interval (D35, D49). Each treatment consisted of 1 ml injected subcutaneously in the limb in 5 x 0.2 ml aliquots (one at each "corner" and one at the centre of a square area of about 5 cm^2).

Monitoring for local and general reactions was performed 1 hour after the injections and for a period of 3 days and then recording of reactions and palpation of the injections sites was performed at least 3 times a week. Post-vaccination rectal temperatures were recorded only in the event that a cat exhibited clinical signs of systemic or local reactions. Skin biopsies from 26 cats were taken 3 weeks after the last vaccination (end of the study) for histological analysis (1 within the centre of the vaccination field and one on the contra-lateral limb). Serological analysis was done prior to treatment and at after completion of the protocol.

One cat died of complications attributable to hypertrophic cardiomyopathy before the last injection. The only post-treatment reactions were transient acute wheal formation in 4 cats following inoculation, resolving spontaneously within hours - all cats remained in good general conditions.

Three weeks after the last vaccination there were normal histological findings in 5/26 cats. All other reactions were confined to minimal or mild subcutaneous infiltration of lymphocytes, histiocytes, plasma and mast cells with minimal to moderate infiltration of lymphocytes and histiocytes into the underlying muscle layer. One cat presented a focal granuloma with refractile material. As the product is not adjuvanted, it is questioned whether this is product-associated - no anomaly in the lymphoid organs.

Cats were confirmed to be seronegative towards canarypox vector at the start of the study – a strong serological response was observed in all cats.

The age of the cats in this study can be considered to be acceptable for testing with regard to mean age at which cats are susceptible to develop a fibrosarcoma. The product was administered as recommended in the SPC so therefore the study can be considered representative of the conditions of use of the product for IL-2 production during a treatment course, despite the fact that only healthy cats were used. The data indicated that some adverse reactions are to be expected during the treatment. Local reactions are limited; this is probably linked to production of small amount of IL-2. This study is relevant to document the safety of the treatment and constitutes additional information to be examined together with field studies performed in target category of cats and involving long-term follow-up.

Safety of overdose and repeated doses of Oncept IL-2 (vCP1338) at maximal titre.

This study was performed in twelve 3-4 months old cats with a product containing vCP1338 at maximum titre. Group 1 consisted of10 treated cats (see administration below) and group 2 of two control cats with no treatment. The administration of Oncept-IL2 was in accordance with the recommended protocol; each treatment consisting in 1 dose injected subcutaneously in the limb in 5x0.2 or 0.3 ml aliquots (one at each “corner” and 1 at the centre of a square area of about 5 cm by 5 cm) plus a rabies dose injected with other components in injection of 1 ml by subcutaneous route at day 56. Investigation of the safety of treatment with Oncept IL-2 administered at the maximal titre and with an overdose as first administration included a clinical examination and weighing from D0 to D56 / biochemistry and haematology at D2, D0, D1, D4 and D14 (blood cell count and dosage of Alanine aminotransferase, alkaline phosphatase, urea, creatinine and total protein). Numeric and graphic descriptive analysis of the data was provided including biochemical and haematological parameters compared to reference values.

Clinical examinations were performed on all cats. After the first overdose injection moderate to marked (up to 40.4°C) and transient (at most 2 days) hyperthermia was found in 8/10 cats. All cats developed apathy on D1, there was however no difference in weight gain between groups. After the overdose mild pain developed in half of the treated cats for 1 to 2 days. Swellings were noted in all cats starting on either D1 or D2 and lasting 2 to 16 days (thickening of the skin less to 1 cm or small nodular reaction / 1 to 3 injection sites). There was a decrease of the local reactions (frequency/size and duration) with number of injections.

No clinically significant variation in haematological or biochemical parameters observed in both groups; only a transient increase of white blood cells at D1 in the treated group as well as transient low decrease of urea not considered clinically relevant.

The product was administered to healthy European cats following the recommended protocol and using a product batch with a maximal titre (first administration at 10 doses followed by 5 administrations; all administrations in 5 injection points). Minor post-vaccination reactions observed consist in inflammations signs; they are classical reactions after administration of a canarypoxvirus and are consistent with reactions described in the SPC. Investigations have focused on parameters known to be markers of acute IL-2 toxicity – haematological parameters, general observation (anorexia, apathy), liver affection, kidney affection (increase uremia and creatinemia), local reactions (pain, inflammation, fever). No significant changes of these parameters have been evidenced. These data suggest that IL-2 which is released at the treatment site should be present at low quantity. Taking into account this new study, the maximal titre proposed by the applicant for Oncept IL-2 is justified.

Overall the CVMP concluded that the two studies investigating safety of the administration of one dose of the product with high titre (10 fold the maximal dose) by subcutaneous route or intravenous route

in SPF cats (8 cats in each treated group) confirm that only mild side effects are to be expected in treated cats, confirming that production of IL-2 by cells after administration of Oncept IL-2 is local, low and transient. The two studies investigating safety of the treatment in 60 healthy conventional cats 14-17 months treated according to the recommended protocol (i.e. 4 treatments at 1-week interval followed by 2 treatments at 2-weeks interval / each treatment consisting in 5 point injections) showed that only mild and transient local reactions were observed during treatment course. Histological analysis confirms observation of mild inflammation at the injection site.

Examination of reproductive performance

No specific reproductive safety test was performed. The CVMP considered this acceptable given the nature and indication of the product as well as the fact that this absence of data in pregnant or lactating animal is mentioned in the SPC.

Examination of immunological functions

Interleukin-2 is an immunomodulator. Data contained in the dossier establish that the treatment leads to production of IL-2 which is local, transient and in low quantities. Efficacy data as well as additional safety data obtained in FIV or FeLV-positive cats demonstrate that after the treatment, there is an activation of the immune system with a effect on recurrence of tumours. Absence of activation of regulation system or auto-immunity is evidenced.

Evaluation of the rabies serological response of one dose of PUREVAX RCPCh mixed with PUREVAX RABIES when administered in the cat after repeated doses of Oncept IL-2 (vCP1338).

This study was performed in twelve 3-4 months old European cats with a product containing vCP1338 at maximum titre. After repeated doses with that product Group 1consisting of 10 treated cats was given PUREVAX RCPCh mixed with PUREVAX RABIES. Group 2 was given no treatment throughout.

Administration of Oncept IL2 was in accordance with the recommended protocol; each treatment consisting in 1 dose injected subcutaneously in the limb in 5x0.2 or 0.3 ml aliquots (one at each “corner” and 1 at the centre of a square area of about 5 cm by 5 cm).

The investigation of the response to the vaccination after Oncept IL-2 treatment included rabies serology at D56, D70 and D84 (anti-rabies FAVN Ab titres).

Group 2 cats remained negative for rabies – all treated cats seronegative before vaccination developed a serological response and showed titres above the recommended protective threshold (0.5 IU/ml).

CVMP conclusion

The CVMP concluded that treatment with Oncept IL-2 does not impair the future response of cats to vaccination. This observation is in accordance with current knowledge on vaccines based on canarypox vector (no evidence of neutralizing antibodies against canarypox virus and no interference of the anti-vector immunity with the efficacy of boosters).

Special requirements for live products

Spread of the product strain

In three studies involving a) 12 SPF cats, b) 12 SPF cats and c) 10 vaccinates as well as 5 controls no vCP1338 was isolated from blood samples, or faecal or pharyngeal swabs of cats injected an overdose

by IV or SC route. and of sentinel cats (not treated) Therefore, no spread of the feline IL-2 canarypoxvirus strain is expected from treated to untreated cats.

Dissemination in the vaccinated animal

In two studies involving a) 12 SPF cats and b) 12 SPF cats no vCP1338 was isolated from blood samples, or faecal or pharyngeal swabs of cats injected an overdose by IV or SC route. Therefore, no dissemination of this recombinant canarypox virus in the body is expected after injection.

This result is fully in accordance with the non-replicative characteristics of the recombinant canarypoxvirus.

Reversion to virulence of attenuated products

The studies conducted for other ALVAC vectors together with the studies conducted in the safety part of this dossier demonstrated that vCP1338 does not propagate in the target species and is not excreted following administration of an overdose. Due to the non-replicative characteristics of the ALVAC virus and derived-recombinant viruses, a scientific advice from the CVMP concerning the reversion to virulence test was asked for another product which contains a recombinant virus vCP97. It was concluded that the test of reversion to virulence was not necessary. The feline IL-2-canarypoxvirus vector (vCP1338) shares the same non-replication characteristics, therefore there is no scientific reason to expect that vCP1338 would behave differently from vCP97.

Therefore the product strain is not likely to revert to virulence through back passages in target animal species. Consequently, the CVMP accepted that no test of reversion to virulence was performed.

Biological properties of the product strain

The *in vitro* replication of the recombinant canarypox virus vCP1338 expressing the gene for IL-2 was studied in avian primary cells, canine cell line, feline cell line, equine cell line, human cell line, canine primary cells, feline primary cells and equine primary cells. Replication was assessed by viral titration during 5 successive passages on each type of cells. vCP1338 did not replicate in any of the 7 mammalian cell types during 5 successive passages, whilst replication was clearly observed in primary chicken embryo cells.

In addition to studies in cats, *in vivo* studies were conducted in the most sensitive species (canaries) and mammalian (dog) to assess the replication ability of vCP1338 in non-target species. The results of these studies confirmed the known properties of the canarypox virus, which have been shown for other products. The CVMP therefore considered that no further studies were necessary.

Recombination or genomic re-assortment of strains

The recombination capabilities of vCP1338 and possible consequences were detailed in the dossier. It is considered that a transfer of genetic material from vCP1338 to another poxvirus is highly unlikely. Recombination between the canarypoxvirus and the cat genome is highly unlikely because the canarypoxvirus replicates in the cytoplasm of the cell and does not enter into the nucleus. There is no difference expected between Oncept IL-2 and other products based on ALVAC recombinant for which this argumentation was already considered acceptable.

In conclusion, genetic transfer and exchange involving an ALVAC vector with other organisms are highly unlikely.

Interactions

No specific interactions with veterinary medicinal products were studied.

The CVMP concluded that this was acceptable but that the absence of information on the compatibility of this product with any other product should be mentioned under 4.8. in the SPC using standard wording.

Field studies

Safety of the treatment has been investigated in real conditions in 23 cats receiving the treatment (Oncept IL-2 formulated with high titres) administered such as recommended: after tumour excision and in addition to radiotherapy (6 administrations - each consisting in 5 point injections). Data demonstrated that the treatment was well tolerated and rare adverse reactions have been observed, consisting mostly in few local reactions (pain, papule or alopecia) and mild general reactions. Long-term investigation over 1 year established absence of long-term immune adverse reactions.

User safety

Oncept IL-2 contains a canarypoxvirus vector expressing feline IL-2.

The safety of the ALVAC vector has been demonstrated in humans. Several ALVAC constructs have been tested in humans in clinical trials in the field of infectious diseases or oncology. Overall, ALVAC-based constructs are well tolerated in humans.

A canarypox virus expressing human IL-2 (ALVAC-huIL2) has been administered in humans in clinical trials. It has been administered by intratumoural route to cancer patients with either metastatic melanoma or cutaneous metastases of primary tumours. The local inflammation induced by the construct was mild and transient and associated with some cases of tumour regression. The treatment was well tolerated.

Although feline IL-2 is a glycoprotein having the same biological function as and sharing sequence homologies with human IL-2, feline IL-2 has poor biological activity in human cells.

This and the fact that ALVAC-huIL2 was safe in humans when administered at more than three-fold the infective titre in a standard dose of Oncept IL-2 provides assurance that Oncept IL-2 does not cause any serious hazard for human health.

The potential user exposure to Oncept IL-2 is considered limited because:

- The end-user is a competent person, i.e. a veterinarian or a trained person under supervision of a veterinarian
- Warnings are included in the outer or immediate package

In assessing accidental self-injection, the following elements are considered:

- The volume to be injected is small (1 ml). Moreover considering the pain induced by the stinging, injecting oneself a whole dose is rather unlikely.
- In case of accidental self-injection, the user is recommended to consult a physician and an appropriate advice has been included in the SPC (section 4.5 “in case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician”).

The CVMP concluded that the user safety of this product is acceptable because safety of the ALVAC vector has been demonstrated in humans and exposure is considered limited because the user will be a veterinarian and the volume treatment is small as well as the fact that appropriate warnings have been included in the SPC.

Environmental risk assessment

Phase I assessment

The environmental risk assessment required by the EU Note for Guidance EMEA/CVMP/074/95 and the assessment required according to Directive 2001/18/EC, Annex II for veterinary medicinal products containing or consisting of GMOs cover more or less identical issues. The environmental risk of Oncept IL-2 was assessed following the recommendations of both documents mentioned above.

A phase I environmental risk assessment was conducted, including a hazard identification and assessment of the exposure to the hazard as well as the likelihood that the hazard may occur. The first phase of the assessment outlines that the potential exposure of the environment to the product and the level of risk associated with it is considered very low to negligible. The likelihood of hazard is very low to negligible and the consequences of the occurrence of any hazard can be considered as negligible. Therefore the estimation of risk can be considered very low to negligible.

Therefore a study of Phase II has not been considered necessary or adequate, due to the very low environmental risk potential of the vaccine.

Environmental risk assessment for products containing or consisting of genetically modified organisms

The product is a live product based on a recombinant canarypoxvirus expressing the feline interleukin-2 (IL-2) gene (vCP1338).

The risk analysis for this product is based on the use of canarypoxvirus strain ALVAC, largely used in already registered products. As a result of the natural host restriction of canarypoxvirus, ALVAC vector and the constructs derived from it do not multiply in the target species (cats) and, more generally, in mammals.

The product will be administered by the subcutaneous route according to the following vaccination schedule:

After reconstitution of the lyophilisate with the solvent, administer one dose of 1 ml, split in five 0.2 ml injections around the tumour excision site (one injection in each corner of the square field and one injection in the centre) according to the following schedule: 4 administrations at 1-week intervals (day 0, day 7, day 14, day 21) followed by 2 administrations a 2-week intervals (day 35, day 49).

A natural property of the canarypox virus is its restricted host range for productive replication to avian species. Consequently, the ALVAC vector and the derivative recombinants were shown not to replicate in tissue culture derived from non-avian species and attempts to adapt the virus for replication by serial passages were unsuccessful. It was specifically demonstrated for vCP1338 both *in vitro* and *in vivo*.

Biochemical studies indicated that the abortive step to viral replication on human cells occurs early in the life cycle of the virus before DNA replication. Following the initial step of cell infection, only early proteins are synthesized.

There is no evidence of any relation between ALVAC vector (DNA virus) and feline IL-2-gene.

The H6 promoter inserted in the recombinant virus is derived from vaccinia virus. There is no report of studies assessing in details the degree of genetic relatedness between canarypox virus and vaccinia virus.

Only the recombination between the ALVAC vector or ALVAC-derived recombinants and another poxvirus is theoretically possible. For a recombination to occur in natural conditions, a simultaneous co-infection in the same cell by 2 poxviruses with some degree of homology is necessary.

Domestic cats may be sporadically infected by poxvirus, particularly by cowpoxvirus (closely related antigenically to vaccinia virus). ALVAC vector and cowpoxvirus belong to the same family (poxviridae) and subfamily (chordopoxviridae) but to different genus (avipoxviridae and orthopoxvirus respectively).

The probability of a recombination between vCP1338 and a poxvirus depends on several factors:

- A superinfection of a cat treated with the ALVAC-derived recombinant by a cowpox virus. Prevalence of cowpox virus in cats is difficult to estimate but serological surveys have shown that only 2 to 4% of the cats have probably been in contact with the virus (Nowotny, 1996 and Yamaguchi, 1996),
- The 2 viruses should co-localise in the same organ. A possibility could be a lymph node infection. The probability is considered low because of the prevalence of the infection in cats,
- The two viruses should co-localise in the same cell. This is statistically very unlikely; moreover viral infected cells defence mechanisms (such as interferon production) reduces the possibility of infection by a 2nd virus,
- The low homology at DNA level between ortho and avipox viruses reduces the risk of recombination. In addition the probability that such an event would lead to a strain with a selective advantage over the infecting cowpox virus seems very low.

In conclusion, the likelihood of recombination between the ALVAC-feline IL-2 and another poxvirus is very low.

Recombination between a canarypox virus (DNA virus) and feline interleukin-2 gene is unlikely to happen because canarypoxvirus replication occurs strictly in the cytoplasm of the cell.

The overall genetic stability of vCP1338 following 10 passages *in vitro* was confirmed by restriction endonuclease analysis, southern blotting analysis and sequencing. Western blot and immunoplaque assays were used to demonstrate expression of donor gene products and phenotypic stability after these 10 passages.

All data to establish compliance of the product with Directive 2001/18/EC have been provided. These data have been already assessed and approved for previous applications. In addition, the history of use of these recombinants has proven the safety of the constructs. It is accepted that the level of risk is very low, given that:

- the genetic construct is stable;
- the narrow host range of the canarypox vector;
- the product does not replicate in mammalian cells;
- it is safe in canaries;
- the product is not shed to any significant extent;
- replication and persistence are limited;
- ALVAC vectored products are already in extensive use apparently without adverse consequence;
- the potential for environmental contamination and spread is low.

Overall conclusion on safety

Safety studies have been performed investigating safety of the administration of the product used at high dose, used by intravenous route or used according to the recommended protocol. Studies on the safety of the administration of 10 doses of Oncept IL-2 by SC route or intravenous route – even if not representative of the recommended treatment - demonstrate that few adverse reactions whether local or general are observed in treated cats. Investigations have focused on parameters known to be markers of acute IL-2 toxicity – hematological parameters, general observation (anorexia, apathy), liver affection, kidney affection (increase uremia and creatinemia), local reactions (pain, inflammation, fever). These data suggest that IL-2 which is released at the treatment site should be present at low quantity.

Two laboratory studies involving cats receiving the recommended protocol namely 6 administrations, each administration consisting in 5 injections and one field study involving up to 2 years investigation of 48 treated cats confirm safety of the treatment with observation during treatment of moderate and transient local and general side effects. These reactions as transient apathy and hyperthermia and possible diarrhoea or vomiting and moderate local reactions disappearing spontaneously within 1 week are rare and may be considered acceptable reactions for a treatment for cats. These reactions have been adequately reported in the SPC.

Two studies performed with the same construct in FeLV and FIV infected cats as well as field safety and efficacy studies confirm the efficacy of the IL-2 recombinant canarypoxvirus in stimulating local immunity and exclude activation of the regulatory system and tolerance system after treatment. One study investigating the response to vaccination against rabies using a recombinant canarypoxvirus vaccine performed 1 week after completion of the treatment with Oncept IL-2 confirms that the treatment will not impair future protective response of cats to vaccination.

Activity of the product to be considered is linked with IL-2 which will be produced *in situ*. No data are available on the maximal quantity of IL-2 that could be produced after treatment nor on any duration nor kinetics of production. It is shown through isolation data that the production remains local, transient (disappearance of the virus and the gene) and in low quantity. Safety studies have been performed demonstrating that the treatment is well tolerated and that only few and mild undesirable reactions whatever local or general are observed in treated cats. Long-term safety issues can be excluded based on the studies provided.

Absence of data on repetition of the whole treatment or on safety of an overdose of IL-2 (which is difficult to define considering nature and method of administration of the product) are not considered issues regarding the indication of the product (administration by veterinarians – indication restricted to cats under radiotherapy) and are stated in the SPC.

The CVMP concluded that the user safety of this product is acceptable because safety of the ALVAC vector has been demonstrated in humans and exposure is considered limited because the user will be a veterinarian and the volume treatment is small as well as the fact that appropriate warnings have been included in the SPC.

Regarding the environmental risk assessment, the first phase outlines that the potential exposure of the environment to the product and the level of risk associated with it is considered very low to negligible.

Assessment required for veterinary medicinal products containing or consisting of genetically modified organisms:: In addition to the requirements of Directive 2001/82/EC as amended, Annex III A of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms

applies for this vaccine. All points to be considered for a live genetically modified organism used as vaccine strain have been addressed.

All data to establish compliance of the product with Directive 2001/18/EC have been provided. It is accepted that the level of risk is very low, given that:

- the genetic construct is stable;
- the narrow host range of the canary pox vector;
- the product does not replicate in mammalian cells;
- it is safe in canaries;
- the product is not shed to any significant extent;
- replication and persistence are limited;
- ALVAC vectored products are already in extensive use apparently without adverse consequence;
- the potential for environmental contamination and spread is low.

Overall, the CVMP considered that the safety of Oncept IL-2 has been satisfactorily demonstrated.

Part 4 – Efficacy

Oncept IL-2 is an immunological veterinary medicinal product containing a recombinant canarypoxvirus expressing feline interleukin-2 (vCP1338). The product is intended to be used as an immunotherapy to be associated with surgery and radiotherapy in order to reduce the risk of tumour recurrence and metastasis in cats with fibrosarcoma. The product activity is effected via the stimulation by the expressed interleukin-2 (IL-2) cytokine of a local immune response against tumour cells at the inoculation site. It is intended to be used after resection of the tumour by surgery as an adjunct treatment, alongside radiotherapy.

Feline interleukin-2 is a relatively small glycoprotein produced by activated T lymphocytes with the same biological functions as interleukin-2 in other species. The gene has been sequenced and shown to code for a 154 aminoacid protein sequence. The choice of development based on a canarypoxvirus vector (ALVAC) for local gene delivery of feline IL-2 was motivated by several reasons: prior evidence of the efficacy of IL-2 against cat fibrosarcoma, absence of replication and dissemination of canarypox vectored vaccine in mammals, intrinsic immunostimulating properties of the canarypox vector, long experience of safe use of canarypox vectored vaccines already on the market, know-how in MERIAL on vectored vaccines and more especially recombinant poxviruses.

Intended use – fibrosarcoma

Feline fibrosarcoma are aggressive cutaneous mesenchymal tumours with a fast growth and possible evolution towards necrosis and ulceration. These are reported to be among the most frequent tumours in the cat (12 to 25% of the skin tumours) occurring in adult cats of any age (mean age 9.5 years – intervals 3-16 years). These tumours infrequently disseminate metastases (metastases may be observed in 6 to 25% of affected cats) but the main issue is their ability to deeply infiltrate adjacent tissues. The first intention treatment consists of large surgical excision of the tumour and surrounding tissues. Local recurrences are frequent (30 to 75%). Post-operative adjunct radiotherapy has been reported to improve prognosis but recurrences still occur at a high rate.

As feline fibrosarcoma is easily accessible for intra- or peri-tumoural injection, it has been used as an animal model for the evaluation of anticancer drugs.

Surgery is the reference treatment of fibrosarcoma. Surgical removing may be difficult, it should be the largest possible and is reported to be associated with 60-80% of relapse within 6 months and 75-92% of relapse within 2 years. Prognostic indicators include size of the tumour, lack of metastases and tumour-free margins. Radiotherapy allows to decrease relapse rate: bibliographic data based on 200 cats followed during 2 years report relapse rates of 34% at 6 months, 58% at 1 year, 66% at 18 months and 75% at 2 years with a median survival of 853 days. Survival time and disease free interval are reported to be significantly influenced by the time between surgery and radiation therapy, tumour size and existence of metastases.

Interleukin-2 in cancer immunotherapy

Interleukin-2 is a glycoprotein secreted by activated T lymphocytes. It was first identified as a soluble factor stimulating the proliferation of lymphoblasts *in vivo*. It is nowadays known to be involved in many different functions, activating or down-regulating the immune response depending on the environment in which it operates. As an enhancer of the immune response, IL-2 is a promoter of B and T cells proliferation, maturation of cytotoxic T lymphocytes (CTL) and lymphokine activated killer (LAK) cells, activation and proliferation of natural killer (NK) cells and immunoglobulins synthesis. IL-2 induces a cytokine cascade with increased production of Tumour necrosis factor, interferons and interleukins.

Data support the role of IL-2in T-reg cell production and homeostasis and essential functions during immune responses at the level of memory response. Thus IL-2 is critical to both the induction and the resolution of inflammatory immune response.

These functions are the basis for the development of recombinant interleukin treatments in human patients with renal carcinoma and metastatic melanoma. Durable clinical response has been observed in a small fraction of IL-2 treated patients. However, the applications for systemic recombinant IL-2 are limited by the severe toxicity of the cytokine in the dose range required to achieve clinical response.

Local IL-2 therapy was shown to be efficacious and safe in various tumour models using recombinant IL-2 and IL-2 gene delivery by different vectors. Direct effects of IL-2 on tumour cells have not been reported.

Direct intratumoural delivery in animals of a replication-deficient adenovirus vector harbouring the murine interleukin-2 gene causes complete disappearance of P815 murine mastocytoma tumours in up to 75% of cases. Histological analysis of treated tumours revealed the presence of several zones of necrosis and the infiltration by macrophages and T cells. Moreover, the successfully treated animals developed a long lasting state of immunity during which further challenged with the tumour cells are rejected. Therapeutic use of IL-2 can generate antitumour immunity; however a variety of different mechanisms have been reported. In mice, it was shown that IL-2 mediated responses were dependent upon tumour size, not on the duration of the disease. IL-2 did not alter tumour antigens presentations in draining lymph nodes. It enhanced a previously primed endogenous tumour-specific CTL response that coincided with regression tumours. Both CD4 and CD8 cells were required.

In a clinical trial performed in human cancer patients with skin tumours, intratumoural delivery of a canarypox virus vector (ALVAC) expressing human interleukin-2 induced significant levels of IL-2 expression and an immune response at the tumour site.

In some cases, unexpected absence of efficacy has been observed in treated patients, which is nowadays attributed to the possible role of IL-2 in increasing Treg cells. Prevention of induction of tumour-specific T-cell responses due to IL-2 may explain the limited efficacy of IL-2 in many cases when used as anti-tumour therapy. Newly revealed functions of IL-2 need to be carefully considered in future use of IL-2 directed therapies: besides promoting Treg cells, 2 other issues are the auto-inhibitory loop where IL-2 inhibits its own production and the capacity of IL-2 to antagonize

development of auto-aggressive Th17 cells. These points have to be taken into account when assessing treatment based on IL-2.

IL-2 is an important T cell stimulatory cytokine approved as exogenous antitumor agent. Overall the mechanism of action should mainly rely on the stimulation of CD8+ and CD4+ T cells, NK cells and production of other cytokine like interferon gamma. Although local IL-2 therapy is a non-specific immunotherapy, it may stimulate tumour-specific immune responses which in some cases may have an effect on untreated metastases.

Interleukin-2 fibrosarcoma immunotherapy

It was shown in highly metastasic melanoma of the dogs and low metastasic fibrosarcoma of the cat that both dogs and cats when treated by tumour surgery, radiotherapy and repeated local injections of xenogeneic Vero cells secreting high levels of IL-2 relapse less frequently and survive longer than control animals treated by surgery and radiotherapy alone. Local secretion of IL-2 by xenogeneic cells is shown to be necessary for the induction of an optimal antitumour effect. Nevertheless, in treated cats, an increase of development of metastases was unexpectedly observed.

In 2003, a group of cats with spontaneous fibrosarcoma were treated either with canarypox virus vector ALVAC or the genetically attenuated vaccinia virus vector NYVAC-based recombinants expressing feline or human IL-2 respectively. These cats receiving IL-2 showed less tumour recurrence (28% and 39% respectively) than the controls not receiving immunotherapy (61%) following treatment with surgery and iridium-based radiation therapy.

Laboratory trials

IL-2 expression in cats after subcutaneous injection of a canarypoxvirus vector expressing feline IL-2 (vCP1338) – effect of the dose and the number of injections

This study was performed in twenty eight 8-10 months old cats randomised into 7 groups based on sex and litter and after they had been previously anaesthetised and clipped in the injections zone located in the interscapular region with a product containing vCP1338 at several doses injected either in 1 or 5 points.

Systemic IL-2 quantification (blood samples - ELISA - D0+12 hours)as well as local IL-2 quantification (local biopsies of injection points - RT-PCR / D0+12h) and blood cell monitoring (before Day 0, D0+12h) was performed.

Additionally a qualitative analysis of the red blood cells and systemic IL-2 production was performed.

Statistical analysis was done of the quantity of IL-2 in biopsies using a 2-ways ANOVA with taking into account factors dose and injection effects.

No effect of vCP1338 injection was found on the blood cell number whatever the dose and the injection procedure. No IL-2 could be detected in the serum with the available technique.

There was a strong dose-effect relationship in cats injected in 5 sites (contrary to cats injected in one site) - a higher quantity of IL-2 was produced locally after 5 SC injections of 0.2 ml than after a single injection of 1 ml of vCP1338vCP1338, whatever the dose.

The level of local production of IL-2 was demonstrated to be dose dependent. No laboratory studies are presented to confirm that the proposed titre results in optimal levels of IL-2 for efficacy for the proposed indication and target species, but the proposed dose follows that described by Jourdier et al (2003) and reference to published literature in support of dose justification is acceptable for a MUMS application (EMA/CVMP/IWP/123243/2006-Rev.2). Additionally, if this dose dependent effect on local

IL-2 production occurs in the target population of cats with fibrosarcoma, it does not appear to result in a difference in efficacy for the proposed indication.

One study has been performed focusing on the expression of interleukin-2 *in vivo* during treatment course in SPF cats receiving different doses administered either at one point or at 5 points. This study confirms the local production of interleukin-2 and the relevance of performing 5 point injections for administration of the product. Although information on the maximal quantity of IL-2 produced, on the kinetic of production and on the mechanisms of action of ILIL-2are not available, such data are not deemed necessary to assess efficacy of the product.

Field trials

There is no experimental model of feline fibrosarcoma, therefore the efficacy of treatment was evaluated directly in the field in cats with spontaneously occurring fibrosarcomas. Two field trials were performed at the same centre over the same period. For safety evaluation, cats were also administered a high dose where fibrosarcoma recurrence was recorded as well. An analysis of the compiled results of both trials was performed for evaluation of any effect of the treatment dose on the clinical response to treatment.

Evaluation of the efficacy of Oncept IL-2 product as an adjunct treatment against feline fibrosarcoma following removal of the tumour and radiotherapy

The study involved 48 cats presented to a French veterinary cancer centre “Centre de cancérologie vétérinaire” for a radiotherapy treatment after surgical excision of a first occurrence of fibrosarcoma that did not have detectable lymph node involvement or metastases prior to inclusion in the study.

Cats were randomized into an Oncept IL-2 treatment group (25 cats) and a control group (23 cats) based on the completeness of tumour excision (assessed by histological analysis of the excision margins).

These cats are presented in details below.

Group A: control group: 23 cats receiving post-operative radiotherapy on D1 and D3.

Group B: treated group: 25 cats receiving radiotherapy on D1 and D3 associated to the administration of 6 successive low doses of Oncept IL-2 (D0, D7, D14, D21, D35 and D49).

Each administration was managed as 5 injections point of approximately 0.2 ml around the surgical site (1 aliquot at each corner of a 5x5 cm square area surrounding the surgical scar and one at the centre). The treatment was performed using Oncept IL-2, freeze-dried product reconstituted in water for injection achieving an administered low titre (less than $^{6.55}EAID_{50}$/ml).

Monitoring of local recurrence and metastasis was performed as well as physical examination every 3 months, CT scansCT of the tumour area and thorax at 3, 6, 12 and 24 months after treatment. Monitoring was discontinued 2 years after treatment.

Efficacy criteria chosen were: for each cat, the date of diagnosed relapse (local recurrence and/or metastasis) was reported for analysis. The relapse rates during 1 or 2 years post-treatment were calculated and the 2 groups were compared based on this criterion.

There was also an investigation of the haematological and biochemical parameters for safety reasons.

Statistical significance for comparability of the groups was checked on following criteria: types of surgical margins (X2 test) and interval between surgery and inclusion (t-test).

Efficacy criteria: The median time to relapse was estimated in both groups. The relapse-free curves (survival curves) were calculated for both groups and analysed. Cats without relapse at study completion and cats lost to follow-up were censored for this analysis.

Interval time between surgery and radiotherapy and the type of surgical margin are 2 factors considered as risk factors of recurrence of fibrosarcoma. Comparability of the 2 treatment groups on these critical factors was checked and assessed.

No impact on the treatment on biochemical and haematological parameters and no clinically relevant safety issue were observed. Efficacy data are described below.

Inclusion criteria: first occurrence of fibrosarcoma – radiotherapy treatment after surgical removal / tumour in any area allowing injection treatment / tumour size between 2-5 cm / histological evaluation of the tumour / no pulmonary metastasis / no enlarged lymph nodes / no local recurrence.

Exclusion criteria: previous adjunct treatment / corticosteroid treatment within 1 week (short acting) or 1 month (long-acting) / tumour size not known or not between 2-5 cm / metastasis / medical conditions that could compromise the cat prognosis.

23 cats were enrolled in control group and 25 in treated group – It was not possible to detect any differences between groups for the distribution of surgical margins defined by histology (there were more cats with dirty surgical margins at histology than with clean ones – about 50 to 60% in both groups) – it was not possible to detect any significant difference between groups for the estimated interval between surgery and radiotherapy treatment – this interval ranged from 12 to 82 days. 5 cats were removed from the trial before relapse for various reasons. Data on these cats are provided as well as justification of exclusion of these cats (all these cats were from treated group– 1 accidental death, 2 developments of a fibrosarcoma at a new location, development of a primary liver tumour and of a diabetes). All other cats were followed-up until relapse or at least for two years after D0. The owners of the cats were blinded to the treatment group. The investigator was not blinded as control cats were not injected with a placebo treatment in order to avoid any potential trauma that could be linked to increase of recurrence (considering hypothesis that frequent injections may be linked to development of fibrosarcoma).

Preliminary examination: complete physical examination including rectal temperature, auscultation, abdominal palpation, examination of eyes, ears and oral cavity, palpation of the surgical scar and lymph nodes,, FIV/FeLV testing, biochemical profile (urea, creatinine, total protein, alkaline phosphatase, alanine aminotransferase), blood count, urine specific gravity, CTCT scan of the tumour area and thorax.

Radiotherapy treatment: on day one, 2 chucks were implanted subcutaneously under general anaesthesia, and placed in parallel on both sides of the scar. A source of radioactive iridium was connected to the chucks during a time necessary to deliver 60 grays on the tumour bed twice on day 1 and twice on day 3.

Few minor adverse events were reported in cats treated with the product. They were classical minor adverse events experienced in most clinical trials. No impact of the Oncept IL-2 treatment on biochemical and haematological parameters was evidenced.

Relapse rate – 1 year

For evaluation of the one-year relapse rate identified as recurrence or metastasis, five cats were excluded from the analysis as they were removed from the study before relapse. In the treated group (group B) a total of 5 of 20 cats (25%) showed a relapse. Of these, 3 cats were observed with recurrence and 2 with metastasis. In the control group (group A) a total of 12 of 23 cats (52.2%) showed a relapse. Of these, 9 cats were observed with recurrence and 3 with metastasis. There was

a trend towards statistical significance (p=0.076). The relapse rate tended to be significantly reduced in Oncept IL-2 treated cats.

Relapse rate – 2 years

For evaluation of the two-year relapse rate identified as recurrence or metastasis, three cats which had not relapsed were lost to follow-up after the 12 month examination. In the treated group (group B) a total of 5 of 18 cats (27.8%) showed a relapse. Of these, 3 cats were observed with recurrence and 2 with metastasis. In the control group (group A) a total of 13 of 22 cats (59.1%) showed a relapse. Of these, 10 cats were observed with recurrence and 3 with metastasis. There was a trend towards statistical significance (p=0.053) for reduction in relapse rate in Oncept IL-2 treated cats compared with controls.

The baseline frequency of relapse observed in control cats in this study is similar to the prior observations and in accordance with the literature (30 to 70%).

Relapse-free interval

The analysis included all the 48 cats i.e. all cats showing recurrence and/or metastasis, all cats with at least 1-year of follow-up exhibiting no relapse or cats removed from the study before relapse. Of these 48 cats, 5 cats of 25 in the treated group and 13 cats of 23 in the control group showed a relapse. Eight cats removed from the trial before relapse were censored for this analysis. The median relapse free interval was 9 months (287 days) for the control group whereas it could not be defined precisely for the treated group but was longer than 24 months (>730 days).

The stratified analysis showed a significant effect of the treatment (p=0.048) with a relapse risk increased in the control group compared to the treated group from day 180 and beyond. The risk ratio indicated that treatment reduced the hazard of relapse by about 65% compared to non-treated cats.

CVMP conclusion

The CVMP noted that four cats included in the treated group were removed within 1 to 3 months after inclusion and beginning of the treatment: 2 cats presented with a new fibrosarcoma in a new site (which the available evidence indicated was not a relapse), 1 cat presented a liver tumoral process (for which diagnosis of primary liver tumour although not confirmed by histology could be acknowledged as the most clinically plausible diagnosis) and 1 cat developed diabetes mellitus. The validity of censoring of these cats after careful examination was accepted. The study is a long term study – 6 years duration with 2 years investigation for each enrolled cat – and involved testing of the product under real recommended conditions. Cats were from different origins and were all enrolled and followed in a unique site location – at the “centre de cancérologie vétérinaire”. 25 cats were treated and compared to 23 cats that underwent surgery and radiotherapy only. Efficacy criteria were based on observation of relapse and metastases (rate and relapse-free interval). Most cfor2 years. In this study, cats received a product dose below the one mentioned in the SPC.

Four treated cats received prohibited concurrent treatment injections (antibiotic therapy or corticoid treatment) during the 2 years follow-up and according to original protocol should have been censored for analysis. After examination of data of these cats, it was accepted that it was valid to take these results into account in the final analysis as they are representative of the true field situation. Additionally, inclusion of these cats also increases the statistical power of the efficacy analysis.

Statistical analysis of the data relies on particular statistical tests based on analysis of “survival data”. Investigation of the cats is limited during time to 2 years as it is not possible to investigate all cats until observation of relapse or natural death. The parameter under investigation i.e. “relapse” was not observed in all cats after 2 years. In this case, in order to explore data such as “relapse-free interval” these cats shall be “censored”. Censored cats (live cats included in the study without relapse at

2 years) are different from removed cats (removing for different justified causes) and distinct from censored cats for which information is not available at the end of the study. Estimation of such data (time without relapse, relapse rate) rely on Kaplan Meier techniques involving curves and Cox models as used by the applicant. Although relapse rate was initially recorded as a primary efficacy endpoint in the original protocol, it was agreed by CVMP that time before relapse (or relapse free interval) supports the same beneficial effect of the treatment, is a classical efficacy endpoint in oncology and allows a more powerful analysis as it includes the data of censored animals.

During 1 year observation, results are not significant (a trend to significance is not conclusive) probably linked to the low number of animals. During 2 years observation period, analysis shows a significant effect of the treatment with an increase of the relapse risk in the control group. As results are significant, calculation of the hazard ratio is relevant and indicates that the treatment reduced the hazard of relapse by about 65% during the 2 years observation period.

Evaluation of safety and efficacy of Oncept IL-2 product as an adjunct treatment against feline fibrosarcoma following surgical removal of the tumour and radiotherapy.

This study is a complement of the previous one involving one additional group initially included for safety evaluation (maximal titre for recombinant canarypoxvirus in the product) but same efficacy investigation was performed in this treated group. Control group was the same as the one described in the report above.

The study involved 46 cats presented to a French veterinary cancer centre “Centre de cancérologie vétérinaire” for a radiotherapy treatment after surgical excision of a first occurrence of fibrosarcoma that did not have detectable lymph node involvement or metastasis prior to inclusion in the study.

Cats were randomized into an Oncept IL-2 treatment group (23 cats) and a control group (23 cats) based on the completeness of tumour excision (assessed by histological analysis of the excisions margins).

Group A: control group: 23 cats receiving post-operative radiotherapy on D1 and D3.

Group C: treated group: 23 cats receiving radiotherapy on D1 and D3 associated to the administration of 6 successive low doses of Oncept IL-2 (D0, D7, D14, D21, D35 and D49). Each administration was managed as 5 injections of approximately 0.2 ml (1 aliquot at each corner of a 5x5 cm square area surrounding the surgical scar and one at the centre).

The product administered was Oncept IL-2 – freeze-dried product reconstituted in water for injections to achieve an administered titre close to the maximum dose.

Investigation of local and general reactions post-treatment and haematological/biochemical parameters for safety issue: see safety part.

Monitoring of local recurrence and metastases – physical examination every 3 months, CT of the tumour area and thorax at 3, 6, 12 months after treatment.

Monitoring was discontinued 1 year after treatment.

For each cat, the date of diagnosed relapse (local recurrence and/or metastasis) was reported for analysis. The relapse rate and the relapse-free interval during 1 year was calculated and the 2 groups were compared based on these criteria.

Statistical significance based on 2-tailed tests of the null hypothesis resulting in p-values of 0.05 or less –for comparability of the groups was checked on following criteria: types of surgical margins and interval between surgery and inclusion (t-test)risk-factors of recurrence of fibrosarcoma).

The median time to relapse was estimated in both groups. The relapse-free curves (survival curves) were calculated for both groups and analysed. Cats without relapse at study completion and cats lost to follow-up were censored for this analysis.

Relapse rate – 1 year

At one year in the study, a total of 19 of 46 cats showed a relapse identified as recurrence and/or metastases. In the treated group (group C) a total of 7 of 23 cats (30.4%) showed a relapse. Of these, 4 cats were observed with recurrence only, 1 with metastasis and 2 with both recurrence and metastasis. In the control group (group A) a total of 12 of 23 cats (52.2%) showed a relapse. Of these, 9 cats were observed with recurrence and 3 with metastasis. None (0) showed both recurrence and metastasis. No significant association between the treatment and the relapse rate was observed.

Relapse-free interval

Of the 46 cats, 7 cats of 23 in the treated group (group C) and 12 cats of 23 in the control group (group A) showed a relapse. The following cats were censored for this analysis: cats for which relapse had not yet occurred at the end of the monitoring period (n=26). The median relapse free interval was 9 months (287 days) for the control group whereas for the treated group it exceeded one year (>365 days). With a relapse risk that tended to increase after 180 days in the controls; the stratified analysis showed a trend towards statistical significance in the difference between the 2 groups (p=0.099). While not significant, the hazard ratio indicated that the treatment reduced the hazard relapse by about 54% compared to non-treated cats.

The CVMP observed that this study was performed using the same protocol as the one described previously. The only difference is the use of the treatment at higher dose (higher titre for canarypox virus that could normally leads to higher production of local IL-2).

As this study was mainly performed for safety purposes, investigations were limited to 1 year follow-up. Despite administration of the treatment at higher dose, (7.3 to 8.28 log10 TCID50) no significant effect of the treatment could be evidenced. This could nevertheless be linked to the low number of animals or the shortest investigation period. No firm conclusion could be drawn from this study.

Evaluation of the efficacy of Oncept IL-2 product as an adjunct treatment against feline fibrosarcoma following surgical removal of the tumour and radiotherapy one year after treatment

This document consists in the consolidation and analysis of the data from the 2 studies outlined above to assess the efficacy of the proposed treatment.

The data from the 2 trials were compiled. Analysis of compiled data is valid since cats were enrolled at the same centre and allocated into either study by a single randomisation process. Investigation was exactly the same in the 2 studies.

The study involved71 cats presented to a French veterinary cancer centre “Centre de cancérologie vétérinaire” for a radiotherapy treatment after surgical excision of a first occurrence of fibrosarcoma that did not have detectable lymph node involvement or metastases prior to inclusion in the study.

Group A: control group: 23 cats receiving post-operative radiotherapy on D1 and D3

Group B: low dose treated group: 25 cats receiving radiotherapy on D1 and D3 associated to the administration of 6 successive low doses of Oncept IL-2 (D0, D7, D14, D21, D35 and D49). Each administration was managed as 5 injections of approximately 0.2 ml. (1 aliquot at each corner of a5x5 cm square area surrounding the surgical scar and one at the centre).

Group C: high dose treated group: 23 cats receiving radiotherapy on D1 and D3 associated to the administration of 6 successive high doses of Oncept IL-2 (D0, D7, D14, D21, D35 and D49). Each administration was managed as 5 injections of approximately 0.2 ml. (1 aliquot at each corner of a 5x5 cm square area surrounding the surgical scar and one at the centre).

The product administered was Oncept IL-2 – freeze-dried product reconstituted in water for injections to achieve an administered titre between $10^{5.86}$and $10^{8.28}$ $EAID_{50}$/ml from 4 different batches.

Monitoring of local recurrence and metastasis was performed as well as physical examination every 3 months, CT scans of the tumour area and thorax at 3, 6, 12 months after treatment.

Monitoring was discontinued 1 year after treatment.

For each cat, the date of diagnosed relapse (local recurrence and/or metastases) was reported for analysis. The relapse rate and the relapse-free interval during 1 year were calculated and the 2 groups were compared based on these criteria.

Statistical significance for comparability of the groups was checked on following criteria: types of surgical margins and interval between surgery and inclusion (t-test) (risk-factors of recurrence of fibrosarcoma).

The frequency of cats that had a recurrence or metastasis after 1 year follow-up was calculatedThe association between the relapse rate and the treatment group. The same analysis was performed with groups B and C pooled together.

A stratified cox regression model was applied to the data with group (A, B and C) as covariate (the type of surgical margin was the stratification variable). The hazard ratio was given. The same analysis was performed with groups B and C pooled together.

Relapse rate – 1 year

At one year in the study, a total of 24 of 66 cats showed a relapse identified as recurrence and/or metastases. In the treated low-dose group (group B) a total of 5 of 20 cats (25%) showed a relapse. Of these, 3 cats were observed with recurrence only, 2 with metastasis and none (0) with both recurrence and metastasis. In the treated high-dose group (group C) a total of 7 of 23 cats (30.4%) showed a relapse. Of these, 4 cats were observed with recurrence only, 1 with metastasis and 2 with both recurrence and metastasis. In the control group (group A) a total of 12 of 23 cats (52.2%) showed a relapse. Of these, 9 cats were observed with recurrence and 3 with metastasis. None (0) showed both recurrence and metastasis. No significant association between the treatment and the relapse rate was observed (while controlling by the type of surgical margin) There was no dose-effect treatment. When groups B and C were pooled together, a total of 12 of 43 cats (27.9%) showed a relapse. Of these, 7 cats were observed with recurrence only, 3 with metastasis and 2 with both recurrence and metastasis. When groups B and C were pooled together, a trend to significant association was observed with a lower relapse rate in treated cats (p=0.05252).

Relapse-free interval

Of the 71 cats, 5 cats of25 in the treated low-dose group (group B), 7 cats of 23 in the treated high-dose group (group C) and 12 cats of 23 in the control group (group A) showed a relapse. The following cats were censored for this analysis: cats removed from the trial before relapse (n=5), cats for which relapse had not yet occurred at the end of the 1 year monitoring period (n=40). The median relapse free interval was 9 months (287 days) for the control group whereas for both treated groups it exceeded the monitoring period i.e. one year (>365 days).

Despite a relapse risk that tended to increase after 180 days in the controls; the stratified analysis did not show a significant effect of the type of treatment when comparing all the groups (Cox model

stratified analysis, p=0.127). When treated groups (groups B and C) were pooled together, a significant treatment effect is observed (p=0.045). The risk ratio indicated that treatment whatever the dose reduced significantly the risk of relapse by about 56% compared to non-treated cats.

The CVMP noted that this report is a compilation of the 2 studies presented above.

Addition of data of both studies for analysis is acceptable insofar as the only difference in the treatment protocol is the titre of the product: inclusion criteria, exclusion criteria, treatment protocols, efficacy endpoints are exactly the same and investigation was conducted by the same persons at the same veterinary clinic. In the analysis, no treatment effect between the two treated groups was demonstrated.

The relapse rate at one year (pooled data, groups B and C) was reduced in treated cats compared with controls (52.2% compared with 27.9%, respectively) and the difference between the groups was close to significance, p=0.052. The relapse free interval between treated cats (pooled data) compared with controls was statistically significant at one year, although only narrowly (p=0.045). During 1 year of follow-up the hazard of relapse was 56% lower in treated (pooled data) compared with non-treated cats. This is considered important information for prescribers and has been included in the SPC.

Pooling of data from the two treatment groups (groups B and C) increased the statistical power of the analysis compared with study at low dose only. A larger sample size could have led to a clearer comparison of efficacy between treated and non-treated cats. However, the difficulty of recruiting large numbers of animals with a low-prevalence disease is recognised, and as this is assessed as a MUMS application, efficacy was considered to have been satisfactorily demonstrated.

Overall conclusion on efficacy

Oncept IL-2 is an immunological veterinary medicinal product but is not a classical vaccine as it is not intended for prophylactic use nor to stimulate specific active immunity.

The requirements in Annex I of Directive 2001/82/EC were used as a guide where applicable.

There is no experimental challenge model of feline fibrosarcoma and the efficacy of Oncept IL-2 was investigated in field conditions in adult cats of various age, sex and breed.

Oncept IL-2 is an immunostimulant treatment intended as complementary immunotherapy to be used in association with surgery and radiotherapy in cats diagnosed with fibrosarcoma without any metastases to reduce the risk of relapse and increase the time to relapse (local recurrence or metastasis). The product is to be administered in cats which will undergo radiotherapy within 1 month after surgical excision, beginning the treatment course the day before radiation therapy. The treatment consists in 6 product administrations: 4 administrations at 1 week interval followed by 2 administrations at 2 weeks interval. Each administration consists in 5 injections of the product around the tumour excision site and in the centre.

It is underlined that the use of such a product in practice will be currently limited to clinics with equipment for radiotherapy or which will refer treated cats to a radiotherapy centre, which represents a limited market in Europe.

Efficacy of the treatment has been demonstrated in a field study involving 48 cats receiving this adjunct treatment according to the recommended protocol compared to 23 control cats and followed during 1 year for recurrence of fibrosarcoma and for observation of metastasis. For25 treated cats, investigation was prolonged for 2 years.

Efficacy of the treatment to significantly reduce the hazard of relapse (recurrence or metastasis) by 56% after 1 year and by 65% after 2 years and to increase time to relapse has been demonstrated in the treated cats during the observation period.

Few data are available in the dossier on the mechanisms of action of such treatment and of *in vivo* production of interleukin-2 after administration of the construct which constitute the basis of this product.

Complete monitoring of the expression of the transgene has not been performed and, in absence of specific method, titration of IL-2 in *vivo* is considered quite complex.

The following information can be obtained from literature that complete the dossier data (Younes et al in journal of pharmaceutical sciences, 2009): Whereas IL-2 based treatment have been tested in many cancer cases in human field, little is still known on the concentration required in the local environment to observe efficacy. It has been established in almost all reported cases that a single IL-2 injection whatever the way (local or systemic) is not sufficient and that there is a requirement for frequent repeated injections of IL-2. The approved IL-2 cancer therapy protocol requires a dosing schedule of intravenous administrations every 8 hours for 5 days followed by another 5 days course after day 9. Standard local immunotherapy with IL-2 includes local injections for 5 consecutive days. IL-2 is acid sensitive and shows stability problems, which requires achievement of a localised sustained release while controlling the dose of this cytokine which may present serious undesirable adverse reactions if not correctly managed. The use of a virus vector expressing IL-2 – in particular a non-replicating, non integrating virus – presents the advantage to allow a temporary continuous local delivery of small amounts IL-2 in the tumour site, which should mimic the cytokine release pattern.

Although the recommended protocol is not fully justified and optimized, the available data nevertheless show a beneficial effect when Oncept IL-2 is used as described in the SPC. Asking for additional data on this point would generate long and difficult amount of work, without any guarantees about optimise probabilities.

In the absence of experimental model of feline fibrosarcoma, the key study is a field trial performed in one cancer centre in France. Cats of various age, sex and breed with first occurrence of fibrosarcoma without metastasis and coming for a radiotherapy treatment after surgical removal of the tumour were enrolled.48 cats received the proposed adjunct treatment with Oncept IL-2 administered as recommended compared to 23 control cats. These cats were followed during at least 1 year for relapse (defined as observation of recurrence and/or metastasis) and for 25 treated cats (cats receiving the product with the lowest titre), the investigation was prolonged during 2 years. Efficacy of the treatment to significantly reduce the risk of relapse by 56% after 1 year and by 65% after 2 years and increase in the time to relapse from 287 days to more than 730 days has been demonstrated in the treated cats during the observation period.

The efficacy studies are limited by lack of statistical power, and this is likely to be linked to the difficulty in recruiting a sufficient number of animals for this minor use product. Nevertheless, a clear trend for efficacy was seen in the field data and the efficacy parameters evaluated were either statistically significant or approaching significance (although the limitations associated with restricted statistical power must be born in mind when looking at statistical significance). Given the power limitations of the clinical trials and the acknowledged difficulty in recruiting sufficient numbers of study animals for a minor use indication, the final conclusion on efficacy took into account the other data in part 4, in particular the additional supportive data from a published paper by Jourdier et al (2003). This reported a prospective study with a one year follow-up period which used a similar dose of the same vector and IL-2 combination (vCP1338) as Oncept IL-2, and used a comparable control treatment. The main differences in posology were the number of injections (one per treatment) and the number of treatments (seven over a period of eight weeks) compared with Oncept IL-2 posology

(injection at five sites around excision, four times at one week intervals followed by two at two week intervals). Similar fibrosarcoma recurrence rates in treated and control cats were seen compared with the Oncept clinical trial: recurrence rate of 28% in treated cats vs. 61% in controls (Jourdier) and recurrence rate of 28% in treated cats vs. 52% in controls (Oncept IL-2, pooled data from field study high and low dose treated groups). The number of cats in the Jourdier study were limited (n=18 in each group), but the CVMP considered that the results were supportive of the applicant's field study results.

Taking into account the efficacy results from the applicant's field studies together with the consistent results from the paper by Jourdier et al (2003), as well as proof of concept in other published literature for the anti-tumour effect of IL-2 therapy, an overall conclusion was reached that the data supported the efficacy of Oncept IL-2 as an adjunct treatment for fibrosarcoma in cats.

Overall, the CVMP considered that the efficacy of Oncept IL-2 has been satisfactorily demonstrated.

Part 5 – Benefit-risk assessment

Oncept IL-2 is an immunostimulant treatment intended as immunotherapy to be used in association with surgery and radiotherapy in cats diagnosed with fibrosarcoma to reduce the risk of relapse (recurrence or metastasis) and increase the time of relapse. It is made of a recombinant canarypoxvirus expressing feline IL-2. Local administration of the product in the site of the tumour allows local production of small amount of IL-2 which is intended to participate to stimulation of local anti-tumour immunity.

This is a full application for an adjunct treatment to surgical excision and radiotherapy. It is underlined that the use of such a treatment will be limited as it is restricted to cats which will be treated in clinics with radiotherapy equipment and also in clinical practices referring to a centre of radiotherapy.

Benefit assessment

Direct therapeutic benefits

The benefit of Oncept IL-2 is as an immunotherapy in addition to surgery and radiotherapy in cats with fibrosarcoma (2-5 cm diameter) without metastasis or lymph node involvement in order to reduce the risk of relapse and to increase the time to relapse (local recurrence or metastasis).

This was demonstrated in a field study involving 48 cats coming from multiple veterinary clinics receiving this additional treatment according to the recommended protocol compared to 23 control cats during 1 year follow-up. For 25 treated cats, investigation was prolonged for 2 years. Efficacy of the treatment to reduce the risk of relapse (recurrence or metastasis) by 56% after 1 year and 65% after 2 years and to increase median time to relapse from 287 days to more than 730 days has been demonstrated in the treated cats.

Additional benefits

None

Risk assessment

Many data have been provided on the safety of the canarypoxvirus as vector which are not new as this vector is already used in many vaccines intended for use in cats (target species for Oncept IL-2) but

also for horses, dogs, ferrets and humans. The construct has been shown to be safe in all these species. It does not replicate, nor disseminate in mammals. Replication in birds is transient and limited in time.

Safety data on Oncept IL-2 indirectly confirm that expression of the gene of IL-2 during treatment course is transient and that production of IL-2 is local and at low dose.

No major adverse reactions are observed during treatment that could be linked to acute toxicity of IL-2. Adverse reactions – mild local and general reactions – observed occasionally in treated cats and not specifically related to IL-2 are acceptable reactions. Long term studies up to 2 years confirm the absence of undesirable effect of the treatment that could be revealed long time post-treatment and in particular absence of activation of regulatory immune system.

The user safety of this product is acceptable because safety of the ALVAC vector has been demonstrated in humans and exposure is considered limited. Additionally appropriate warnings have been included in the SPC.

Regarding the environmental risk assessment, the first phase outlines that the potential exposure of the environment to the product and the level of risk associated with it is considered very low to negligible.

In addition to the requirements of Directive 2001/82/EC as amended, Annex III A of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms applies for this vaccine and the CVMP concluded that all points to be considered for a live genetically modified organism used as vaccine strain have been satisfactorily addressed.

Evaluation of the benefit-risk balance

The formulation and manufacture of Oncept IL-2 are well described and specifications set will ensure that product of consistent quality will be produced.

The treatment is well tolerated by the target animals and presents a low risk for users and environment and appropriate warnings have been included in the SPC.

Efficacy of the treatment has been demonstrated in a field study involving 48 cats coming from multiple veterinary clinics receiving this additional treatment according to the recommended protocol compared to 23 control cats during 1 year follow-up. For 25 treated cats, investigation was prolonged for 2 years. Efficacy of the treatment to reduce the risk of relapse (recurrence or metastasis) by 56% after 1 year and 65% after 2 years and to increase median time to relapse from 287 days to more than 730 days has been demonstrated in the treated cats.

The CVMP also took into consideration that the proof of concept for the product as well as efficacy results are supported by published literature and that the existing therapies (surgical excision and radiotherapy) for feline fibrosarcoma are associated with a high risk of recurrence and mortality.

Conclusion on benefit-risk balance

Taking into account the high recurrence rates of fibrosarcoma and a high risk of mortality despite available treatments the proposed treatment with Oncept IL-2 as an adjunct to surgical excision and radiotherapy is supported by results from a pivotal clinical study where a reduction of the risk of relapse (recurrence or metastasis) and an increase of the median time to relapse were demonstrated during a 2-year follow up period and also taking into consideration results from published literature.

Conclusion

Based on the original and complementary data presented the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the data on quality, safety and efficacy of Oncept IL-2 were considered to be in accordance with the requirements of Directive 2001/82/EC, as amended, and that the benefit-risk balance was favourable.