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Veterinary Medicines and Product Data Management

Scientific discussion

This module reflects the initial scientific discussion for the approval of Purevax Rabies (as published in March 2011). For information on changes after this date please refer to module 8 of the EPAR (Steps taken after authorisation).

1. Summary of the dossier

Purevax Rabies is a vaccine indicated for the active immunisation of cats 12 weeks of age and older to prevent mortality due to rabies infection. It is presented in boxes of 10 and 50 vials, each containing a single dose 1 ml vial. The route of administration is subcutaneous use. The target species is cats. Purevax Rabies is eligible for assessment under the centralised procedure by means of article 3(1) and the annex of Regulation (EC) No 726/2004 which refers to veterinary medicinal products developed by means of biotechnological processes such as recombinant DNA technology.

2. Quality

Composition

The vaccine contains a recombinant canarypox virus expressing the rabies glycoprotein G (vCP65) as active ingredient and is a ready-to-use single dose liquid suspension without adjuvant or preservative. The viral titre is determined by titration followed by immunofluorescence. The method is used on both the active ingredient and the final vaccine and is validated.

Container

The product is presented in different packaging sizes, i.e. box of 10 bottles of 1 dose and box of 50 bottles of 1 dose. The bottle is a European Pharmacopoeia (Ph.Eur.) type I glass bottle closed with an elastomer-derived closure and sealed with an aluminium cap. Validation of the sterilisation procedures of the bottle and closure materials is in accordance with Ph.Eur..

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Development pharmaceutics

The information provided on the vaccine strain and its advantage of not being replicative in non-avian species demonstrate the significance of the use of this live recombinant canarypox virus as active ingredient. This leads to the development of a liquid vaccine, including justified choices on antigen concentration and quantification, on diluent, on bottle and closure, and on starting materials.

Method of manufacture

The manufacturing method is a classical vaccine manufacturing process involving growth on chicken embryo fibroblasts prepared from specific pathogen free (SPF) eggs. Three main steps are concerned: 1) preparation of the active substance, 2) preparation of the filled vaccine and 3) packaging of the finished product. The process is well described. The batch size of the active substance ranges and the batch size of the finished product ranges were described.

Control of starting materials

Active substance

The vCP65 virus seeds used in production of the antigen are well characterised and control testing according to the Ph.Eur. is considered sufficient. Antigen lots are manufactured by MERIAL Laboratoire de Lyon Gerland and are tested for sterility and viral titre. Batch-to-batch consistency at production scale is demonstrated through the presentation of batch data.

Real-time stability data are submitted for the active ingredient, which can be stored frozen until its use in formulation of the vaccine. A shelf-life of 27 months can be granted for the vCP65 active ingredient. Validation on the refrigerated transport of the active substance between the different manufacturing sites has been shown in a specific study simulating the environment of this active substance when it is transported and the appropriate temperature was maintained.

Excipients

Certificates of analysis are provided for all excipients used in the manufacture of the vaccine. These materials are tested according to the Ph.Eur. or internal procedures as appropriate. Sterilisation of some materials is performed by filtration instead of by steam sterilisation, as this would either alter their properties or is technically not feasible. Calf serum is tested according to the CVMP guideline on requirements and controls applied to bovine serum used in the production of immunological veterinary medicinal products (EMEA/CVMP/743/00) by general and specific tests for adventitious viruses and the requirements of Ph.Eur. Monograph no. 2262 and is thereafter sterilised by gamma irradiation.

Packaging

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

The starting materials of biological origin either comply with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Rev02) or an acceptable transmissible spongiform encephalopathy (TSE)

risk assessment is given. The overall TSE risk associated with the Purevax Rabies vaccine is deemed negligible.

Control tests during production

The control tests performed during production are clearly indicated and comprise test for sterility and titration of the active ingredient, recording of time and temperature of operations at different stages, filter integrity testing, sterilisation cycle monitoring, filled volume and appearance of the product after capping, labelling and secondary packaging. Results on these parameters are provided for batches at production scale.

Control tests on the finished product

The methods used for the control of the finished product (appearance, pH, volume, identification and titration of vCP65, safety test, bacterial and fungal sterility, mycoplasmic sterility, viral purity) and the specifications are provided. End-of-shelf-life specifications are also proposed. The test methods are deemed adequate to control the vaccine and are appropriately validated. The results of consecutive vaccine lots are presented, showing compliance with the proposed specifications. Batch-to-batch consistency is demonstrated with batches manufactured at production scale.

Stability

Real-time stability data are presented for batches of vaccine stored under its proposed storage conditions, i.e. at 2°C to 8°C, protected from light. A little loss in viral titre is seen, but the currently available stability results support the shelf-life claim of 18 months at 5°C ± 3°C. The vaccine is intended for immediate use after broaching, thus in-use shelf-life is not applicable.

Overall conclusions on quality

It was concluded that the provided data are of an acceptable quality.

3. Safety assessment

Purevax Rabies is a non-adjuvanted monovalent vectored vaccine against rabies in cats. It contains the recombinant canarypox virus vCP65 which expresses the glycoprotein G gene from rabies virus. The vaccination schedule recommends the subcutaneous injection of 1ml dose of vaccine from the age of 12 weeks. An annual booster vaccination is recommended.

Purevax Rabies is not adjuvanted, similar to all vaccines belonging to the Purevax range.

Purevax Rabies is a ready-to-use suspension. It may be used as a diluent for Purevax non-adjuvanted freeze-dried vaccines containing various combinations of feline viral rhinotracheitis (R), calicivirosis (C), panleucopenia (P) and chlamydiosis (Ch) components.

Most studies were carried out using a combined vaccine containing the rabies component vCP65 (Purevax Rabies) as well as herpesvirus, caliciviruses, panleucopenia virus, *Chlamydophila felis* and leukaemia (recombinant canarypox-FeLV, vCP97) components of the Purevax range vaccines. In these studies animals were therefore injected with two canarypox viruses, vCP65 and vCP97.

The safety trials were carried out in the target species i.e. cats, in both young and adult animals. Laboratory studies in cats were performed with animals of at the most the minimal age recommended for vaccination (12 weeks). Some of the trials were carried out in other species (dogs, canaries, chickens and mice).

Safety documentation

Laboratory tests

The maximum vCP65 canarypox-rabies titre $10^{8,3}$ cell culture infectious dose 50% ($CCID_{50}$) has been used in the laboratory studies.

Safety of the administration of one dose

In a good laboratory practice (GLP) study the safety of Purevax Rabies injected simultaneously with the Purevax RCPCh FeLV vaccine was compared to that of the Purevax RCPCh FeLV vaccine alone. SPF kittens, aged 8 weeks, younger than the minimal age recommended for vaccination (12 weeks) were randomly assigned to 2 groups A and B according to their sex and weight at reception. On D0, all injections were administered by the subcutaneous route in the interscapular region. The RCPCh-FeLV-rabies vaccine (pilot batch, 2 ml, mixed vaccine) administered to group A contained maximum contents. Cats from group B were injected with a commercial dose of Purevax RCPCh FeLV vaccine.

No difference between the two vaccinated groups was observed in respect of general conditions, rectal temperature and weight gain. No apathy was observed in any cats during the whole monitoring period. After the injection of RCPCh-FeLV-rabies vaccine, mild and moderate hyperthermia was observed in 50% of the cats 8 hours post-injection. After the injection of Purevax RCPCh FeLV vaccine, one cat presented moderate hyperthermia 8 hours post-injection.

After administration of the RCPCh-FeLV-rabies vaccine, no leukocyte count less than 50% of the initial mean value was observed. Transient swelling, pain, erythema and/or cutaneous heat at injection site were observed in both vaccinated groups. In group A pain was mild to moderate in all but one cat and lasted 1 to 2 days. Swellings observed in all cats from group A (RCPCh-FeLV-rabies) were initially oedematous and then became nodular within 3 to 4 days before disappearing completely between 4 and 14 days post-injection. All local reactions remained moderate and transient. No persistent nodule was observed.

The safety profile was similar in both groups but with more local reactions observed in group A (RCPCh-FeLV-rabies) than in group B (Purevax RCPCh FeLV). This was explained by the difference of total vCP titres tested in both groups (maximum titres in group A vs. standard titres in group B) and by the additional canarypox virus construct (vCP65) present in RCPCh-FeLV-rabies group A in comparison with RCPCh FeLV group B.

No histological examination of injection sites was performed. However histological results were available from a study performed with Purevax RCPCh FeLV including the recombinant canarypox-FeLV where only minor inflammatory reactions were observed.

Safety of one administration of an overdose

In a GLP study the safety of an overdose of the combined RCPCh-FeLV-rabies vaccine was compared to that of the recombinant canarypox-FeLV vCP97 (Purevax FeLV) alone. SPF kittens (younger than the minimal recommended age), were randomly assigned to three groups. In the first group A, cats were injected subcutaneously with an overdose of all components of RCPCh-FeLV-rabies on D0

followed by a single dose with maximal titres of all components on D28. The second group B was injected subcutaneously with an overdose of vCP97 FeLV on D0 followed by a single dose at maximum titre on D28. Cats from the third group C were not vaccinated and served as controls for leukocyte count.

Following overdose, apathy was observed in all cats in group A up to one day post-injection and depressed appearance was observed only once in a small number of cats. These reactions were associated with hyperthermia. The average daily weight gain between D0 and D28 was significantly lower in group A than in group B, which may have been due to the apathy and hyperthermia.

After the injection of an overdose of vaccine, swelling, pain and cutaneous heat at injection site were observed in both vaccinated groups. Prevalence of local reactions was higher in group A than in group B. Following overdose in group A, pain was observed in all but one cat between D0+4 hours post-injection and D3. Pain was slight except in a number of cats for which moderate pain was observed 1 to 3 times. In most cats, pain lasted less than 48 hours.

In group A swelling was present in all vaccinated cats; the initially oedematous reactions became small sized nodules and then disappeared completely within 10 to 19 days post-injection. Cutaneous heat was observed in all cats following the injection. No erythema and no itching were observed.

Most cats in group A had leukocyte counts that were less than 50% of the initial mean value. However one cat assigned to group C (unvaccinated) had a leukocyte count less than 50% of the initial mean value on D10. Decrease in leukocytes counts is expected after vaccination with a live panleucopenia vaccine and especially with a vaccine containing a very high titre of feline panleucopenia virus, explaining the lower values observed in group A. Importantly, leukocytes counts remained within acceptable range. The strongest reduction in leukocyte counts may be the result of the vaccine effect combined with the variability of the count in young animals. Despite these very severe conditions, in all cats decreases in leukocyte counts were transient and had no effect on the general body condition. No significant difference was observed on the leukocyte count 1, 2 and 4 weeks after the second vaccination between groups. There was no evidence of an immunosuppressive effect following the last injection of combined vaccine including the FeLV component. The effects on leukocytes are attributable to the P component of the combined vaccine.

As for the previous study, the vaccine used was of a broader combination (RCPCh-FeLV-rabies) than those recommended (Purevax rabies alone or combined with Purevax RCPCh). The combined RCPCh-FeLV-rabies vaccine was well tolerated after injection of an overdose followed by a single dose injection in SPF kittens. The reactions were similar to the ones observed after the administration of one dose but may last longer.

Safety of the repeated administration of one dose

The safety of the repeated administration of one dose of vaccine was demonstrated in cats, as part of the vaccination schedule used in the study presented in the section above. Indeed, in this trial the administration of an overdose was followed by a repeated administration of one dose. In group A receiving RCPCh-FeLV-rabies very few reactions were recorded as only one cat showed apathy on one occasion. General body condition remained good for all cats injected with FeLV vaccine. Slight pain was observed in a number of cats 4 hours post-injection of RCPCh-FeLV-rabies and one cat presented severe then moderate pain 4 hours and 8 hours post-injection, respectively. Mostly slight swelling was observed in all cats. All swellings were small sized (< 2cm) except for one cat that presented a swelling ≥ 2cm 4 hours post-injection. Reactions generally faded completely within 4 to 8 days. The nature of swelling was oedema except for a number of cats with reactions initially oedematous that became nodular before fading completely. There was no evidence of local reaction in cats injected with FeLV vaccine.

Examination of reproductive performance

No specific study was carried out, as the product will not be recommended for use in pregnant animals.

Examination of immunological functions

It is not expected that Purevax Rabies may have a particular effect on the immunological functions of the animals treated (except for the direct effect of the vaccine leading to efficacy against challenge). Indeed the canarypox vector is not replicative in mammals and is not known for any adverse effect on immunogenicity.

Special requirements for live vaccines

Spread of the vaccine strain

In a reversion to virulence study, no vCP65 could be isolated from conjunctival, nasal and faecal swabs from any of the passages carried out in cats. Therefore no spread of the vaccine strain is expected from vaccinated animals.

Dissemination in the vaccinated animal

In a reversion to virulence study, no vCP65 could be isolated from conjunctival, nasal and faecal swabs from any of the passages carried out in cats. Therefore no dissemination in the body is expected after injection.

Reversion to virulence of attenuated vaccines

Due to the non-replicative characteristics of the canarypox vector and derived-recombinant viruses, scientific advice from the CVMP concerning this test was sought for Purevax FeLV vaccine (formerly Eurifel FeLV) which contains FeLV recombinant virus vCP97, and concluded that the test was not necessary. As the recombinant canarypox-rabies vCP65 has the same characteristics, this conclusion is considered applicable to canarypox-rabies vaccine. Nevertheless a reversion to virulence study was available. Canarypox vector vCP65 did not revert to virulence in seronegative cats. Even injected at high doses, the virus was not excreted. When isolated from the site of inoculation and passaged *in vivo*, vCP65 did not revert to virulence and became undetectable by the 4th passage.

Biological properties of the vaccine strain

Replication particularities

In vitro studies

The *in vitro* replication of the recombinant canarypox virus vCP65 was studied in avian primary cells and in mammalian cell lines from cats, dogs, horses and humans, and compared with that of the parental canarypox virus (CPpp). vCP65 and CPpp did not replicate in any of the four mammalian cell types during six successive passages, whilst multiplication was observed in primary chicken embryo cells for both viruses. Therefore the insertion of the rabies protein G gene did not modify the host specificity of the canarypox virus.

Another *in vitro* study was designed to determine whether the recombinant canarypox virus vCP65 or the parental canarypox virus (CPpp) could be adapted to growth in two mammalian cell lines. Multiplication of vCP65 and CPpp was tested in three different cell types, from chickens, monkeys and humans. vCP65 and CPpp did not replicate in any of the two mammalian cell types during ten

successive passages, whilst multiplication was observed in primary chicken embryo cells for both viruses with no loss of titre. In simian cells, levels of virus fall below the level of detection after two passages for CPpp and one passage for vCP65. In human cells, neither virus was directly detected after passage 1. There was no evidence of adaptation of either virus to growth in simian or human cells. Therefore the insertion of the Rabies protein G gene did not modify the host specificity of the canarypox virus.

In vivo studies

Cats

In a reversion to virulence study, no vCP65 could be isolated from conjunctival, nasal and faecal swabs from any of the passages carried out in cats. This confirms *in vivo* the absence of replication of vCP65 in mammalians.

Dogs

A study was performed to investigate the excretion of recombinant canarypox viruses expressing therapeutic and/or prophylactic genes in dogs after parenteral administration. Pups were subcutaneously injected with recombinant canarypox viruses containing an overdose. Several recombinants were administered at separate injection sites. Blood was collected from the dogs prior to inoculation and after inoculation. Urine and rectal swabs were taken after administration of the constructs. All samples were titrated for the presence of canarypox-virus by successive passages on primary chicken embryo fibroblast cells. None of the samples was tested positive for recombinant canarypox-virus, confirming *in vivo* the absence of replication of vCP65 in mammalians.

Chickens

In a study, chickens were inoculated with vCP65 using three different routes. The inoculation sites never demonstrated a pox "take" and necropsy did not show any untoward reactions or any signs of gross lesions consistent with pox virus infection. This shows that whereas vCP65 replicates *in vitro* in chicken primary cells, there is no evidence of replication *in vivo* in chicks.

Safety for various species

The ALVAC vector (a highly attenuated poxvirus strain derived from the canarypox virus) and/or many derived recombinants have been studied for more than 20 years. They were tested in many animal species, either avian or mammalian, as well as in humans, and safety was always shown to be satisfactory.

Recombination or genomic reassortment of the strains

The recombination capabilities of vCP65 and possible consequences were detailed in the dossier.

Potential for genetic transfer and exchange between poxviruses

Only the recombination between the ALVAC vector or an ALVAC-derived recombinant (such as vCP65) and another poxvirus is theoretically possible. The construction of the vCP65 itself is based upon an *in vitro* homologous recombination. However, for an *in vivo* recombination to occur in natural conditions, a simultaneous co-infection in the same cell by 2 poxviruses with some degree of homology is necessary. This is highly unlikely to happen in the conditions of dissemination.

Potential for genetic transfer and exchange with a virus related to the donor organism

Recombination between a canarypox virus (DNA virus) and a rabies virus (RNA virus) is highly unlikely to happen because of the different nature of the nucleic acids. In addition, canarypox and rabies viruses do not infect the same cells. In conclusion, genetic transfer and exchange involving an ALVAC vector or the genetically modified organism (GMO) with other organisms is highly unlikely.

Study of residues

The target species is cats. Therefore there is no consumer safety issue. The vaccine is formulated without adjuvants. The recombinant rabies-canarypox is non-replicative in mammals. There are therefore no issues regarding the injection site.

Interactions

The safety of Purevax Rabies has been tested in a multivalent environment constituted of MERIAL feline viral rhinotracheitis, calicivirosis, panleucopenia, chlamydiosis and leukaemia components (see sections above). Because of possible serological interferences with the leukaemia component, the applicant has chosen to limit the use to the non-adjuvanted MERIAL feline viral rhinotracheitis, calicivirosis, panleucopenia, chlamydiosis Purevax range of vaccines.

Field studies

In field trials, the vaccine used came from batches whose titre was slightly lower than the maximum titre.

Primovaccination

The safety of primo-vaccination was studied under field conditions, in accordance with good clinical practice (GCP) principles in a large scale randomised multicentric trial. Purevax Rabies was administered in combination with Purevax RCPCh FeLV (containing the FeLV, Rhinotracheitis, Calicivirosis, Panleucopenia and Chlamydia components). The safety was compared with the Purevax RCPCh FeLV vaccine administered alone.

The sample size comprised cats from various breeds and ages, with a significant number of cats aged 12 weeks or less at inclusion. One group of cats was injected with the test vaccine (Purevax RCPCh FeLV mixed with Purevax rabies), and another group with the Purevax RCPCh FeLV vaccine only. Both vaccines were injected by the subcutaneous route. Four weeks later, all cats were injected with Purevax RCPCh FeLV vaccine in order to complete the primary vaccination course.

No statistically significant difference was observed between treatments for the rate of immediate general reaction. Only a very small number of cats injected with Purevax RCPCh FeLV-rabies vaccine presented a change of behaviour or vomiting. These adverse reactions were probably related to stress (handling, transport to the veterinary practice) and pain associated to the injection rather than to the vaccine itself. They lasted a few minutes and did not require any treatment.

Delayed general reactions were significantly more frequent in cats injected with Purevax RCPCh FeLV-rabies vaccine (24.5%) than in cats injected with Purevax RCPCh FeLV (14.2%)**.** In both groups, most of these reactions were apathy (19.8% of cats injected with Purevax RCPCh FeLV-rabies, and 10.8% of cats injected with Purevax RCPCh FeLV). Anorexia was reported in 8.0% of cats injected with Purevax RCPCh FeLV-rabies vaccine and in 2.8% of cats injected with Purevax RCPCh FeLV. Most of the apathy and/or anorexia reaction lasted 2 days or less. Other symptoms (mainly

vomiting and/or diarrhoea) were reported in 8.0% of cats injected with Purevax RCPCh FeLV-rabies vaccine and in 4.5% of cats injected with Purevax RCPCh FeLV vaccine. All cats except one injected with Purevax RCPCh FeLV-rabies vaccine recovered from delayed general reactions without treatment. These delayed reactions may be attributable to the *Chlamydia* component.

No statistically significant difference was observed between both treatments (Purevax RCPCh FeLV-rabies and Purevax RCPCh FeLV) for the rate of immediate local reaction. Immediate local reactions were mainly transient itching for cats injected with Purevax RCPCh FeLV-rabies vaccine and transient pain for cats injected with Purevax RCPCh FeLV vaccine. All reactions lasted a few minutes and disappeared without treatment.

No statistically significant difference was observed between treatments (Purevax RCPCh FeLV-rabies and Purevax RCPCh FeLV) for the rate of local delayed reaction. The most frequent local reaction observed was pain or swelling for Purevax RCPCh FeLV-rabies vaccine, and pain for Purevax RCPCh FeLV vaccine. Most reactions lasted few days and did not require any treatment.

A swelling reaction was observed in a very small number of cats injected with Purevax RCPCh FeLV-rabies vaccine and none in cats injected with Purevax RCPCh FeLV vaccine. All but one swelling reactions were noticed during the first days following the injection and disappeared within 1 to 3 days. One swelling reaction disappeared within 45 days post-injection.

The reactions observed with both products are of the same nature, only the frequency of the delayed general reactions is slightly higher with the Purevax RCPCh FeLV-rabies vaccine.

Another GCP randomised multicentric trial was performed using a similar design addressing the safety of primo-vaccination of Purevax Rabies when administered in combination with Purevax RCPCh FeLV in cats. The sample size comprised cats aged 5 months on average. On D0, one group of 39 cats was injected with Purevax RCPCh FeLV mixed with Purevax rabies vaccine (group A), and another group with the Purevax RCPCh FeLV vaccine (group B). All vaccines were injected by the subcutaneous route. On D28, all cats were injected with Purevax RCPCh FeLV vaccine in order to complete the primary vaccination course.

There was no immediate general reaction in cats injected with Purevax RCPCh FeLV-rabies or Purevax RCPCh FeLV. No statistically significant difference was observed between treatments (Purevax RCPCh FeLV-rabies and Purevax RCPCh FeLV) for the rate of delayed general reaction. In both groups, most reactions were apathy and/or hyperthermia. These reactions usually lasted less than 2 days and did not require any treatment. Other symptoms (diarrhoea or respiratory symptoms) were occasionally observed in both groups. All adverse reactions observed were moderate and did not seriously affect the general condition of the animals. The delayed reactions may be attributable to the *Chlamydia* component.

No statistically significant difference was observed between treatments (Purevax RCPCh FeLV-rabies and Purevax RCPCh FeLV) for the rate of immediate local reaction. Only one cat injected with Purevax RCPCh FeLV presented pain. No immediate adverse reaction was observed in cats injected with Purevax RCPCh FeLV-rabies. No delayed local adverse reaction was observed in cats injected with the Purevax RCPCh FeLV-rabies.

Following the injection of Purevax RCPCh FeLV vaccine, a small number of cats showed a slight and transient pain, and in one of those cats, pain was associated with a transient small swelling reaction. All reactions disappeared without any treatment within 1 or 2 days.

The safety profile of the Purevax RCPCh FeLV-rabies vaccine was found to be at least as good as that of the Purevax RCPCh FeLV vaccine.

Booster vaccination

The field safety study of a Purevax Rabies when administered in combination with Purevax RCPCh FeLV in cats as an annual booster was studied in a GCP large scale randomised multicentric trial**.** The sample size comprised cats aged 5 years on average already vaccinated against rabies. The cats were allocated on D0 either to group A who received Purevax RCPCh FeLV-rabies, or to group B who received Purevax RCPCh FeLV. All vaccines were injected by the subcutaneous route.

There was no immediate general reaction in cats injected with Purevax RCPCh FeLV-rabies. Only 1 cat injected with Purevax RCPCh FeLV presented a shock 15 minutes after the injection. The cat was injected with corticosteroids and recovered within 30 minutes.

Most reactions, in both groups (84% for Purevax RCPCh FeLV-rabies and 64% for Purevax RCPCh FeLV) appeared during the 3 days following the vaccine injection. However, in both groups, a few reactions (16% for Purevax RCPCh FeLV-rabies and 36% for Purevax RCPCh FeLV) were observed more than one week after the injection but they disappeared within 2 to 8 days. In both groups, most of the delayed general reactions were apathy: 16.3% for cats injected with Purevax RCPCh FeLV-rabies, and 9.5% for cats vaccinated with Purevax RCPCh FeLV. Anorexia was reported in 5.3% of cats injected with Purevax RCPCh FeLV-rabies vaccine and in 1.1% of cats injected with Purevax RCPCh FeLV. Other symptoms (mainly musculoskeletal or digestive disorders) were reported in 2.1% of cats injected with Purevax RCPCh FeLV-rabies vaccine and in 4.2% of cats injected with Purevax RCPCh FeLV vaccine. In the group injected with Purevax RCPCh FeLV-rabies vaccine, most of the apathy and/or anorexia reactions (74%) disappeared within 2 days. Only 1.6% of cats injected with Purevax RCPCh FeLV-rabies vaccine were treated (1 shot of non-steroidal anti-inflammatory or administration of corticosteroids for 10 days) for at least apathy and/or anorexia. Only 2.1% of cats injected with Purevax RCPCh FeLV vaccine were treated for at least apathy and anorexia (1 shot of non-steroidal anti-inflammatory). No statistically significant difference was observed between treatments for the rate of delayed general reaction (16.8% versus 12.6%).

No statistically significant difference was observed between treatments for the rate of immediate local reaction (1.6% versus 1.1%). Immediate local reactions were mainly transient pain and/or itching for cats injected with Purevax RCPCh FeLV-rabies vaccine, and transient pain for cats injected with Purevax RCPCh FeLV vaccine. All reactions lasted a few minutes and disappeared without treatment. No statistically significant difference was observed between treatments for the rate of delayed local reaction. In both groups, delayed local reactions were mainly pain at the injection site. All delayed local reactions disappeared within a few days without treatment except for 1 cat.

Of the cats injected with Purevax RCPCh FeLV-rabies vaccine, only 1 that presented depilation and itching at the injection site was administered with an injection of corticosteroids.

Swelling reaction was observed in 1.1% of cats injected with Purevax RCPCh FeLV-rabies vaccine and none in cats injected with Purevax RCPCh FeLV vaccine. These swelling reactions were small-sized and not painful. One was a small non-painful deep induration at the injection site and 10 months later this induration could be still palpated and the size was the same.

The adverse reactions observed in this field trial were of the same nature as those observed in the laboratory safety studies.

Large scale use in North America

vCP65 strain contained in Purevax Rabies is already used in another vaccine Purevax Feline Rabies launched in the USA (1998) and in Canada (2000). Pharmacovigilance data collected from the large scale use of this similar vaccine since its launch in North America were provided to support the

safety assessment of Purevax Rabies. Data show that the safety of vCP65-based vaccines is satisfactory and as expected.

During the period January 2004 - June 2009, the incidence rates of pharmacovigilance cases considered probably (A-assessed) or possibly (B-assessed) linked with the use of the vaccine indicate that overall the adverse events are very rare (0.47 adverse events and 0.56 animals affected per 10,000 doses).

The most common clinical signs in cases assessed as causality observed in A and B cases included in decreasing order general signs such as lethargy, hyperthermia/pyrexia, anorexia, vomiting, allergic manifestations, diarrhoea, lameness or death as well as local signs such as pain or oedema. Such signs are expected and well known in feline vaccinology and correspond to what can be expected from experience with the canarypox technology in cats. The incidence rates for these signs show that the adverse events are very rare (less than 0.3 adverse events per 10,000 doses even for the most common signs).

User safety

Purevax Rabies can be considered safe for humans. The potential user exposure is considered limited. In case of accidental self-injection, the volume to be injected is small (1ml). ALVAC-based vaccine candidates were demonstrated to be safe in humans. In case of accidental self-injection, the user is recommended to consult a physician. USA and Canadian pharmacovigilance data from 2004 to 2009 show an incidence rate of 0.009 cases per 10,000 doses which is very low. A warning is included in the summary of product characteristics (SPC) as follows: *"Canarypox recombinants are known to be safe for humans. Mild local and/or systemic adverse reactions related to the injection itself may be observed transitorily. In case of accidental self-injection, seek medical advice immediately and show this package insert or the label to the physician".*

Environmental risk assessment

Hazard identification

Purevax Rabies is intended for use in domestic cats. After injection in cats, due to the non-replicative properties of the strain in mammalian cells, no dissemination exists in vaccinated animals and the vaccine strain is not shed in the environment. Therefore the virus will not be in contact with the environment. Transmission to susceptible birds is limited (narrow host range) and would necessitate close contact between the recombinant vaccine strain and canaries. Therefore the capacity to transmit is extremely low. The pathogenicity of the vaccine strain was tested in canaries and did not show any evidence of pathogenicity. As far as species other than canaries are concerned, vCP65 is non-replicative and safe. The inserted sequences code for structural glycoprotein G of rabies without known or suspected harmful effect in animals or humans. In summary, no hazard exists.

Assessment of likelihood

Purevax Rabies is manufactured and delivered in tightly-closed vials. It will be administered on prescription only, and only by a veterinary surgeon or by a trained person under supervision of a veterinary surgeon. The risk of direct release of the vaccine to the environment is therefore limited. In addition, no shedding is possible from vaccinated cats as Purevax Rabies is non-replicative in this species. Safe disposal of used containers or shelf-life expired containers should be assured because the vaccine administration will be carried out by or under the supervision of a veterinarian. Consequently the likelihood of hazard can be considered negligible.

Assessment of the consequence
If, by accident, Purevax Rabies was released directly into the environment (e.g. accidentally broken bottle), the virus could only affect canaries and was demonstrated safe in this species. The consequence of hazard is low or negligible.

Assessment of level of risk
Considering the negligible likelihood of hazard and the low or negligible consequence of hazard, the level of risk for the environment is effectively zero.

Assessment of the overall risk to the environment
As a result of all the previous assessments and characteristics of the product, it appears that the overall risk is effectively zero.

Control measures
As a conclusion of the estimation of risk, it appears that no particular precaution has to be taken. However it is necessary to avoid any unnecessary release and to comply with the national regulations in force regarding waste disposal. Therefore there is no need to proceed to a phase II assessment.

Overall conclusion on safety

It was concluded that the provided safety data are acceptable.

Based on a review of all adverse events observed in the laboratory and field trials, the following information has been included in section 4.6 of the SPC:

"Transient and slight apathy may occur, as well as occasionally mild anorexia or hyperthermia (above 39.5°C), lasting usually 1 or 2 days. Most of these reactions appeared during the 2 days following the vaccine injection.

A transient local reaction may occasionally occur (pain at palpation, limited swelling that may become nodular, heat at the injection site, and in some cases erythema), that usually disappears within 1 or 2 weeks at most.

Very rarely, a hypersensitivity reaction may occur, which may require appropriate symptomatic treatment."

Purevax Rabies can be considered safe for humans. The potential user exposure is considered limited. In case of accidental self-injection, the user is recommended to consult a physician. A warning is included in the SPC as follows: *"Canarypox recombinants are known to be safe for humans. Mild local and/or systemic adverse reactions related to the injection itself may be observed transitorily. In case of accidental self-injection, seek medical advice immediately and show this package insert or the label to the physician".*

The overall risk to the environment is considered negligible.

Based on the safety data of this dossier, the safety profile for the target species cats, for the user and for the environment is considered acceptable.

4. Efficacy assessment

Purevax Rabies is a non-adjuvanted monovalent vectored vaccine against rabies in cats. It is a ready-to-use suspension for injection containing the recombinant canarypox virus vCP65 which expresses the glycoprotein G gene from Rabies virus. The vaccination schedule recommends the subcutaneous injection of 1ml dose of vaccine from the age of 12 weeks. An annual booster vaccination is recommended. Purevax Rabies aims at completing the current non-adjuvanted Purevax range as it may be used as a diluent for Purevax freeze-dried vaccines containing various combinations of feline rhinotracheitis (R), calicivirosis (C), panleucopenia (P) and chlamydiosis (Ch) components.

The Ph.Eur. Monograph no. 451 "*Vaccinum rabiei inactivatum ad usum veterinarium*", even if not fully appropriate (targeting inactivated vaccine), was used as a guide for efficacy.

Tests were carried out in the feline species, in young and adult animals, both in laboratory and in field conditions. Animals unvaccinated against rabies served as controls. The Purevax Rabies dose used in all efficacy trials had a volume of 1 ml which is the claimed volume quantity for a dose of this product. Vaccines were administered via the recommended route of administration, i.e. the subcutaneous route. The antigen content tested in challenge studies was the minimal quantity of antigen claimed for Purevax Rabies, i.e. 6.8 $\log_{10}$ 50% fluorescent antibody infectious dose ($FAID_{50}$) of vCP65 per dose. The influence of maternally derived antibodies has not been studied given the minimal age recommended for vaccination of 12 weeks. The applicant has provided information supporting decline of maternally derived antibodies to very low levels at 3 months of age.

Laboratory trials

Immediate efficacy of Purevax Rabies was tested when injected simultaneously with R, C, P and Ch components against a rabies challenge in cats. SPF kittens, aged 11 weeks on average were randomly assigned to two groups and were vaccinated either with Purevax Rabies mixed with RCPCh vaccine, or with Purevax RCPCh vaccine (controls). Kittens were challenged with a rabies strain 4 weeks later.

All controls developed typical clinical signs of rabies, and presence of rabies virus was confirmed in their brains. In the rabies vaccinated group of cats, over the 3 months following the challenge, only one cat developed clinical signs evocative of rabies. The diagnosis of rabies in the brain was negative for all the other vaccinated cats.

All controls remained seronegative until the challenge day. All vaccinated cats developed anti-rabies antibodies after vaccination. After the challenge, a booster effect was observed in most rabies vaccinated cats. The rabies vaccinated cat that developed clinical signs showed a lower antibody titre on the challenge day.

It was concluded that at a minimal dose, the rabies component mixed with R, C, P and Ch components efficiently protected kittens against a rabies challenge as soon as 4 weeks after vaccination.

The duration of protection was evaluated in another study where efficacy of the RCPCh-FeLV-rabies vaccine against a rabies challenge in cats was carried out one year after primary vaccination. SPF kittens were randomly assigned to two groups. At inclusion, cats from the first group were vaccinated subcutaneously with a RCPCh-FeLV vaccine mixed with Purevax Rabies, then they received Purevax RCPCh FeLV vaccine 4 weeks later. Cats from the other group were vaccinated twice with Purevax RCPCh FeLV vaccine at a 4-week interval and served as controls. Kittens were challenged 13 months later with a rabies strain.

Rabies challenge was validated as all controls remained seronegative until the challenge day, they developed typical signs of rabies after challenge and presence of rabies virus was confirmed in their brains. In the rabies vaccinated group, two cats developed clinical signs evocative of rabies. Presence of rabies virus was confirmed in their brains. No rabies virus was found in the brains of the remaining cats that remained healthy 3 months after challenge.

All rabies vaccinated cats developed rabies antibodies after vaccination, while all controls remained seronegative until the challenge day. The two rabies vaccinated cats that developed clinical signs after challenge showed lower antibody titres on the day of challenge.

This study demonstrated that at a minimal dose of the RCPCh-FeLV-rabies vaccine efficiently protected against a rabies challenge carried out more than 1 year after the vaccination and induced an active immunisation against rabies.

Another study with Purevax Rabies in cats was initiated and the animal phase is still on going. An interim report presented the kinetics of anti-rabies antibodies, from the primary-vaccination to about 1 year after the annual booster.

SPF kittens were randomly assigned to three treatment groups, A, B and C. At inclusion, all cats were vaccinated with RCPCh FeLV components at one site by subcutaneous route. Three weeks later, cats from group A were vaccinated with Purevax Rabies mixed with RCPCh components and injected at one site and FeLV component was injected at a different site. Cats from group B were vaccinated with Purevax Rabies injected at one site and RCPCh FeLV components injected at a different site. Cats from group C were vaccinated with RCPCh FeLV components injected at one site (control group). More than one year after the primary-vaccination (13 months), all cats received a booster injection. Cats from group A and B were vaccinated with Purevax Rabies injected at one site and RCPCh FeLV components injected at a different site. Cats from group C were vaccinated with RCPCh FeLV components injected at one site. Following 14-month blood sampling, some cats from groups A and B were kept in the study forming the vaccinated group D.

All cats from the control group C remained negative for rabies throughout the study. A primary injection of Purevax Rabies induced a significant seroconversion in all cats and rabies antibody titre remained relatively stable for one year. The booster injection of Purevax Rabies one year after the primary vaccination induced a booster effect on rabies antibody titre and titres remained relatively stable for about one additional year.

Purevax Rabies is recommended to be used as a diluent for all or part of the Purevax freeze-dried components R, C, P and Ch. Therefore efficacy of each of these components was fully tested in appropriate challenge studies. Product tested in these studies was the multivalent RCPCh-FeLV-rabies vaccine. Results obtained with this larger combination are valid as the latter contains the same components except for the presence of the FeLV component.

Results are compliant with the requirements of respective monographs of the Ph.Eur..

Immediate efficacy of the RCPCh-FeLV-rabies vaccine against an FHV challenge was tested in cats. SPF kittens were randomly assigned to two groups. Cats from the first group were vaccinated first with RCPCh-FeLV-rabies vaccine, then with RCPChFeLV vaccine 4 weeks later. Seven days after the second vaccine injection, all cats were challenged with a virulent FHV strain. Cats from the other group were not vaccinated and served as controls. They were challenged in the same time as the vaccinated group.

Following challenge, all controls showed typical clinical signs of herpesvirus disease. The mean score for general symptoms (rectal temperature and body condition) was lower in the vaccinated group than in the control group. In the vaccinates, mild hyperthermia was only detected on one occasion in a low number of cats and the challenge had a limited impact on the weight gain of the cats. Some

clinical signs were present in the vaccinates but both mean global and local scores were highly reduced in the vaccinated group compared to the control group. Virus shedding was significantly reduced in the vaccinated group.

It was concluded that vaccination with the minimal herpesvirus titre conferred reduction of clinical signs against a virulent challenge performed 1 week post basic vaccination and that efficacy was not affected by the presence of the rabies vCP65 component.

Immediate efficacy of the RCPCh-FeLV-rabies vaccine against a feline calicivirus challenge in cats was tested in another study. SPF kittens were randomly assigned to two groups. Cats from the first group were vaccinated with RCPCh-FeLV-rabies vaccine and then, 4 weeks later, with RCPCh FeLV vaccine. Cats from the other group were not vaccinated and served as controls for the challenge. Seven days after the second vaccine injection, all cats were challenged with a virulent FCV strain.

The FCV challenge was validated as all controls developed FCV typical signs, such as hyperthermia, oronasal ulceration, weight loss and nasal discharge. The mean global score was very significantly reduced in the vaccinated group. Two vaccinated cats did not show any clinical signs and the others showed only mild symptoms such as mild transient hyperthermia, occasional small oronasal ulcers. One vaccinated cat presented transient large and/or numerous oronasal ulcers and transient nasal discharge. None of the cats shed FCV before challenge. After challenge, FCV was isolated from all cats and viral excretion was significantly lower in the vaccinated group.

It was concluded that vaccination with close to the minimal calicivirus titre conferred reduction of clinical signs and of viral excretion against a virulent challenge performed 1 week post basic vaccination and that efficacy was not affected by the presence of the rabies vCP65 component.

Immediate efficacy of the RCPCh-FeLV-rabies vaccine against a feline panleucopenia challenge was also studied in cats. Kittens were included in the study and randomly assigned to two groups, one group receiving one injection of RCPCh-FeLV-rabies vaccine and the other remaining unvaccinated and served as control. All cats were challenged with a virulent strain of feline panleucopenia virus one week after vaccination.

The feline panleucopenia challenge was very severe. Typical clinical signs of panleucopenia infection were observed in all controls. Challenge induced also a diminution in the number of leukocytes of at least 75% of the initial value in the majority of controls.

Global clinical score was significantly lower in vaccinates than in controls. None of the vaccinates presented a leukocyte count decline greater than 50%, and all remained healthy throughout the study. Only slight or transient signs were observed.

Virus excretion was significantly higher in controls than in vaccinates. All vaccinates presented a low residual viral excretion of the panleucopenia vaccinal strain at time of challenge and the level of excretion remained low post challenge, whereas all controls excreted high titres of panleucopenia virus after challenge.

It was concluded that vaccination with minimal panleucopenia vaccinal titre conferred protection against panleucopenia challenge performed 1 week post one injection while the recommended basic vaccination consists of two injections, 3-4 weeks apart and that efficacy was not affected by the presence of the rabies vCP65 component.

Immediate efficacy of the RCPCh-FeLV-rabies vaccine against a *Chlamydophila felis* challenge was studied in cats. SPF kittens were randomly assigned to two groups. Cats from the first group were vaccinated with RCPCh-FeLV-rabies vaccine, and then with RCPCh FeLV vaccine 4 weeks later. Cats from the other group were not vaccinated and served as controls for the challenge. Seven days after the second vaccine injection, all cats were challenged with a virulent *Chlamydophila felis* strain.

The mean score for general symptoms and the mean global score were lower in the vaccinated group than in the control group. All controls showed typical clinical signs of chlamydiosis, such as hyperthermia, acute conjunctivitis and purulent ocular discharge. Most of the vaccinated cats only showed a slight and transient hyperthermia. The relative weight gain after challenge was significantly higher in the vaccinated group. Ocular symptoms observed in the vaccinated group were less severe than in the control group.

Bacterial shedding was significantly reduced in the vaccinated group. After challenge, controls shed significantly higher quantities of *Chlamydophila felis* and during a longer period than vaccinates.

It was concluded that vaccination with *Chlamydophila* antigen at the minimal dose conferred reduction of clinical signs and of bacterial excretion against a virulent challenge performed 1 week post basic vaccination and that efficacy was not affected by the presence of the rabies vCP65 component.

Field trials

Three different combinations of Purevax Rabies with other components were tested in the field in naive animals (never vaccinated against rabies). Preliminary data suggested that the co-administration of rabies vCP65 and FeLV vCP97 may have an impact on the immunogenicity of Purevax Rabies. This led to another field trial which investigated the rabies serological response when Purevax Rabies was injected in one injection site mixed with R, C, P and Ch components.

Two preliminary field efficacy studies of the primary vaccination with Purevax Rabies either administered mixed with the Purevax RCPCh FeLV or injected mixed with RCPCh at the same site and with FeLV vaccine at a different site, were performed in cats. In these studies, a control group received only Purevax RCPCh FeLV.

A significant increase in rabies antibody titres was observed 14 and 28 days after the injection of Purevax RCPCh FeLV-rabies vaccine. However the absence of a significant increase of rabies antibody titre in some cats when all components were injected led to the third field trial.

The third field efficacy study of the primo-vaccination of the Purevax Rabies when injected in cats simultaneously with RCPCh components, according to the recommended use, was performed in a large scale randomised multicentric trial. In this trial, cats received either Purevax RCPCh-Rabies vaccine, or Purevax RCPCh FeLV.

A significant seroconversion against rabies was observed from 14 days after the primary-vaccination with Purevax RCPCh-Rabies. Globally, a significant increase in rabies antibody titre was observed 14 and 28 days after primary vaccination. The Purevax RCPCh-rabies vaccine, injected in cats as a primary vaccination, under field conditions induced a significant seroconversion against rabies in a higher majority of cats than with the RCPCh-FeLV combinations preliminary tested (Purevax Rabies either mixed with the full combination RCPCh-FeLV or mixed with RCPCh only, whereas FeLV vaccine is injected at a separate site).

Purevax Rabies is the first vectored vaccine against rabies in Europe. Therefore it will be used not only to vaccinate naive cats but also cats already immunised with classical adjuvanted vaccines. Two different combinations of Purevax Rabies with other components were tested in these conditions.

Two field efficacy studies of Purevax Rabies when administered as an annual booster, either simultaneously with Purevax RCPCh FeLV, or simultaneously with RCPCh components and concurrently with FeLV component, was performed in cats. The study objective was to confirm under field conditions the efficacy of the vaccination with the Purevax RCPCh FeLV-rabies vaccine injected in cats already vaccinated against rabies with a conventional inactivated vaccine. Rabies serological

response was monitored for 4 weeks post-injection. In these studies, cats received either Purevax RCPCh FeLV-Rabies, or Purevax RCPCh FeLV only.

Before vaccination, cat populations of both groups were comparable in terms of cat characteristics as well as mean rabies antibody titre. Globally, Purevax RCPCh FeLV-rabies vaccine induced a significant increase of the rabies antibody titre 14 and 28 days after the vaccination. The individual serological response depended on the antibody titre at the time of vaccination. Increase in titre, as expected, was stronger when cats had low antibody titres at the time of booster vaccination.

The trials showed that Purevax Rabies could boost the immune response in cats primed with a conventional inactivated vaccine.

Another field efficacy study of the booster vaccination of the recombinant canarypox-rabies when injected in cats simultaneously with RCPCh components and concurrently with FeLV component was performed in a GCP large scale randomised multicentric trial. The sample size comprised cats aged 6 years on average. Cats were randomly allocated on D0 either to group A who received one dose of RCPCh-rabies vaccine at one site and one dose of FeLV vaccine at a different site, or to group B who received the control vaccine Purevax RCPCh FeLV. Cat populations of both groups were comparable on D0 in terms of cat characteristics as well as mean rabies antibody titre. The injection of Purevax RCPCh FeLV-rabies vaccine induced a statistically significant increase on average between D0 and D14 and between D0 and D28. The individual serological response depended on the antibody titre at the time of vaccination. Indeed, increase in titre, as expected, was stronger when cats had low antibody titres at the time of booster vaccination.

The trial showed that the canarypox-rabies recombinant vaccine could boost the immune response in cats primed with a conventional inactivated vaccine. As previously explained, interference with the canarypox-FeLV may explain the non-booster or low booster response observed in 25% of the cats.

Therefore, as a precaution, it has been decided to amend the SPC to mention that *"Based on currently available efficacy data showing a risk of interference, the administration of Merial non-adjuvanted vaccine against feline leukaemia is not recommended within 14 days before or after vaccination with this vaccine."*

Overall conclusion on efficacy

Based on the data provided, it was concluded that at a dose of $10^{6.8}$ $FAID_{50}$ vCP65 per cat, the rabies component efficiently protected against a rabies challenge as soon as 28 days after the vaccination in 11 week old kittens.

The data provided demonstrated also that at a dose of $10^{6.8}$ $FAID_{50}$ vCP65 efficiently protected against a rabies challenge carried out more than 1 year after the vaccination.

Purevax Rabies is recommended to be used as a diluent for all or part of the Purevax freeze-dried components R, C, P and Ch. Therefore efficacy of each of these components was fully tested in appropriate challenge studies. Product tested in these studies was the multivalent RCPCh-FeLV-rabies vaccine. Immediate efficacy of the RCPCh-FeLV-rabies vaccine against a feline herpesvirus, calicivirus, panleucopenia virus and *Chlamydophila felis* challenges in cats was also tested in GLP studies. It was concluded that efficacy of the four components R, C, P and Ch was not affected by the presence of the vCP65 component.

The influence of maternally derived antibodies has not been studied given the minimal age recommended for vaccination of 12 weeks. Based on the data provided, it can be recommended to use Purevax Rabies as a diluent for all or part of the Purevax freeze-dried components R, C, P and Ch. Overall it was concluded that the provided efficacy data are acceptable.

5. Benefit Risk Assessment

Purevax Rabies is indicated for the active immunisation of cats 12 weeks of age and older to prevent mortality due to rabies infection. It contains the recombinant canarypox virus vCP65 which expresses the glycoprotein G gene from Rabies virus. The route of administration is subcutaneous use. The target species is cats. Annual booster vaccination is recommended.

Benefit assessment

Direct benefits

Efficacy of lowest recommended dose has been demonstrated against rabies challenge 28 days after the vaccination in kittens. One injection is sufficient.

A duration of protection of more than one year after the vaccination against challenge has been demonstrated.

Primary vaccination under field conditions induces a significant increase of anti-rabies antibodies. The vaccine can boost the immune response in cats primed with a conventional inactivated vaccine.

Indirect benefits

It is a ready-to-use suspension that can be mixed with the Purevax freeze-dried range vaccines containing the R, C, P and Ch components.

Additional benefits

It is a non-adjuvanted vaccine.

Risk assessment

Injection of Purevax Rabies combined with RCPCh-FeLV induces mild or moderate hyperthermia. Local reactions consist in swelling, pain, erythema and/or cutaneous heat at injection site. Pain is slight to moderate and may commonly last 1 to 2 days. In some cats, initially oedematous swellings may become nodular. All local reactions are moderate and transient.

Overdose of the same combination induces apathy, hyperthermia and reduction of daily weight gain. Swelling, pain and cutaneous heat at injection site are observed. Swelling is initially oedematous then nodular and disappears completely within 10 to 19 days post-injection. Cutaneous heat resumes within 2 days. The SPC reflects all of the adverse reactions.

The recombinant canarypoxvirus is non-replicative in cats. Therefore there are no issues linked to reversion to virulence and replicative properties. There are no consumer safety issues. The risk to the user is very limited. An appropriate warning is included in the SPC.

Evaluation of the benefit risk balance

The product has been shown to have a positive benefit/risk balance. The efficacy of preventing rabies has been demonstrated. It is well tolerated in cats and presents a low risk for users and the environment.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the Purevax Rabies is approvable.

Based on the data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product are considered to be in accordance with Directive 2001/82/EC, as amended.