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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report of an application for the granting of a community marketing authorisation for Proteq West Nile (EMEA/V/C/002005)

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

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Introduction

An application for the granting of a Community marketing authorisation of Proteq West Nile has been submitted to the Agency on 30 April 2010 by MERIAL in accordance with Regulation (EC) No. 726/2004.

Proteq West Nile contains 1 dose and is presented in packs/containers of box of 1, 2, 5 and 10 vials of 1 dose. The route of administration is intramuscular use. The target species is horses.

Proteq West Nile was confirmed by CVMP to be eligible for the centralised procedure under Article 3 (1) of Regulation (EC) No. 726/2004 as it contains a veterinary medicinal product developed by means of biotechnological processes such as recombinant DNA technology. The CVMP confirmed that the product is considered 'Minor Use or Minor Species/Limited Markets' and that 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.1) is applicable.

Quality assessment

Proteq West Nile is a live recombinant vectored liquid vaccine against West Nile disease. The vaccine consists of canarypox-West Nile virus active ingredient adjuvanted with carbomer. The container is a type I glass vial with a butyl elastomer closure containing one dose.

All the production steps are carried out by MERIAL Laboratories.

The description of manufacturing method is correctly documented and detailed enough to allow the conclusion that it is satisfactory. The active ingredient even if it is a recombinant virus is produced by classical culture on SPF chicken embryo cells. The nature of the raw materials, manufacturing process, controls and treatments applied enable to guarantee sterility of the vaccine and absence of introduction of any extraneous agent, and to guarantee consistency and homogeneity of the production. This is ensured by all the controls performed on the raw materials and the vaccine as well as all the process parameters investigated and recorded during the manufacturing.

The starting materials of animal origin used in the production of the final product comply with the current regulatory texts related to the TSE Note for Guidance on Commission Directive 1999/104/EEC. In conclusion, the risk of transmitting TSE through the vaccine can be considered as extremely low (strain of avian origin, bovine raw materials with low infectivity, high dilution factor).

The results of the analysis of three consecutive production runs of vaccine were presented which comply with the required specifications.

As a whole, the control tests for the product are sufficiently described and validated. They provide a clear picture of the active substance and the finished product. Consistency and homogeneity of the vaccine production is ensured and consequently the quality of the released vaccine batches can be concluded to be satisfactory.

Safety assessment

Target animal safety

Proteq West Nile is a live recombinant canarypox virus that expresses the genes preM/E of the West Nile virus. It is presented as a suspension for injection that contains Carbomer (4 mg/dose) as adjuvant.

The vaccine is intended for immunisation of horses against West Nile disease by reducing the number of viraemic horses. If clinical signs are present their duration and severity are reduced. The vaccination schedule recommends an intramuscular injection of a first dose of 1 ml from the age of 5 months. Four to six weeks later, a second dose of 1 ml has to be injected. An annual booster vaccination is recommended.

The vaccine Proteq West Nile was used in one study in order to demonstrate the safety of an overdose and of the repeated administration of one dose. The batch used contains the maximum antigen amount.

The other safety studies were performed with the vaccine Recombitek Equine West Nile Virus and with ProteqFlu-Te.

The vaccine Recombitek Equine West Nile Virus is a registered vaccine commercialised by MERIAL in North America since 2004. It includes a freeze-dried pellet containing the same components as Proteq West Nile and has to be reconstituted with 4 mg per dose of carbomer adjuvant. In order to improve convenience for the end user of the product in Europe, Merial has developed the ready-to-use liquid vaccine Proteq West Nile.

The vaccine ProteqFlu-Te was also used to support the safety of Proteq West Nile. The composition of the vaccine ProteqFlu-Te is similar to that of Proteq West Nile apart from the canarypox insert and the presence of tetanus toxoid. ProteqFlu-Te is a liquid vaccine containing two recombinant canarypox viruses expressing genes from equine influenza virus, and a carbomer adjuvant. The maximum release titre of the canarypox virus(es) is the same for both vaccines, i.e. 7.8 $\log_{10}$ $CCID_{50}$, the adjuvant quantity is the same (4 mg/ml) and the target species and the administration route are the same, i.e. an intramuscular injection of a 1 ml dose to horses. Hence, ProteqFlu-Te was used in the studies provided to show the absence of impact of the vaccination on reproductive performances and in one of the field trials.

The vaccine Proteq West Nile was demonstrated to be safe after the administration of an overdose (10 times the maximum release titre at D0) and repeated doses (maximum release titre at D28 and D56) to young horses. No severe systemic reactions occurred following injections. After the overdose injection, only a slight transient hyperthermia without impairment of the general condition was observed on one single occasion in some horses. No hyperthermia was reported after the two following administrations on days 28 and 56. Local reactions were mostly minor, *i.e.* only palpable, lasted mostly one day and were resorbed spontaneously. After the third vaccination, some horses showed minor or mild swelling (max diameter 5 cm) for 3 to 4 days. None of the horses showed pain, cutaneous warmth, itching or neck stiffness after each of the three vaccinations.

The safety of the administration of one dose was demonstrated with the vaccine Recombitek Equine West Nile Virus registered in North America and that has the same composition as Proteq West Nile but this vaccine has a freeze dried presentation.

This vaccine was also used to assess the spreading and the dissemination ability of the vaccine strain and to study the safety of the administration to non target species (canaries, crows, mice and mosquitoes).

Given the non-replicative properties of the recombinant canarypoxvirus, no spread, dissemination and reversion to virulence is expected.

The impact on reproductive performances was assessed in four studies including pregnant mares in laboratory and field conditions. The animals were vaccinated with ProteqFlu-Te, which is a liquid vaccine containing two recombinant canarypox viruses expressing genes from equine influenza virus, and a carbomer adjuvant. The maximum release titre of the canarypox virus(es) and the adjuvant quantity are the same as those of Proteq West Nile. The CVMP accepted to accept these substitute studies to support the safety of Proteq West Nile due to the similarities of the vaccines and because the West Nile vaccine is listed 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.1).

No interaction study has been presented. This is reflected in the SPC.

Two field studies were conducted. In the first one, horses were vaccinated with the vaccine Recombitek Equine West Nile Virus. The results confirm that the vaccine is safe and support the results obtained in laboratory conditions. The vaccine batch used was close to the maximum titre and was administered according to the primary vaccination schedule to horses of different ages (part of the animals were 2-4 months old).

The general reactions observed were lethargy/mild depression that were transient (less than two days). These side effects were not observed in the laboratory conditions but are not unexpected.

The local reactions were swellings generally below 5 cm of diameter. They had disappeared generally two weeks post-vaccination.

In the second field trial, the vaccine ProteqFlu-Te containing only the minimum antigenic amount was used. Nevertheless, it demonstrates that ProteqFlu-Te that contains canarypox virus constructs in carbomer adjuvant, similarly to Proteq West Nile, is well tolerated in 6-12 month old foals after a primary vaccination course and a revaccination 6 months later.

Environmental risk assessment

The environmental risk assessment for the genetically modified canarypox virus has been satisfactorily addressed. It was concluded that the vaccine presents a negligible risk to the environment.

The potential for genetic transfer and exchange between poxviruses was also addressed satisfactorily. Only the recombination between the ALVAC vector or an ALVAC-derived recombinant (such as vCP2017) and another poxvirus is theoretically possible. The construction of the vCP2017 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 two poxviruses with some degree of homology is necessary. This is highly unlikely to happen in the conditions of dissemination. Moreover, scientific knowledge to date indicates that poxviruses are unimportant as causes of viral diseases in horses. Altogether, these elements confirm that potential for genetic transfer and exchange between poxviruses is negligible.

Potential for genetic transfer and exchange with a virus related to the donor organism: Recombination between a canarypox virus (DNA virus) and a West Nile virus (RNA virus) is highly unlikely to happen because of the different nature of the nucleic acids.

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

User safety

The user safety of Proteq West Nile was also addressed and concluded to be acceptable based on the following argumentation.

The potential user exposure to Proteq West Nile is considered limited because:

The end-user is a competent person, i.e. a veterinarian or a trained person under supervision of a veterinarian,

Appropriate warnings are included in the outer or immediate package,

In case of accidental self-injection, the following elements must be considered: the volume to be injected is small (1 ml) and considering the pain induced by the stinging, injecting oneself a whole dose is rather unlikely (withdrawal reflex),

ALVAC-based vaccine candidates were demonstrated safe in humans,

In case of accidental self-injection, the user is recommended to consult a physician (cf package leaflet: "In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician").

In the USA and Canada, based on pharmacovigilance data collected between 2004 and 2009, one adverse event in human, mostly following accidental injection, and considered probably or possibly linked with the use of the vaccine or assessed as unclassifiable, has been reported for every 100,000 doses sold.

The CVMP consequently concluded that the user safety assessment showed that the administration of the vaccine does not present a specific risk to the user.

In humans, several ALVAC-based vaccine candidates have been inoculated into volunteers and were found safe (publications provided for ALVAC rabies (Fries 1996, Taylor 1994), ALVAC-HIV (Jin 2002), ALVAC-CMV (Adler 1999) and ALVAC-JEV (Kanesa-Thasan 2001).

Study of residues

Residue aspects were also addressed adequately. Considering that Proteq West Nile is a non-replicative live vectored vaccines (where no MRL is necessary) and its adjuvant, carbomer (a common name for all carbopol derivatives) is considered by the CVMP as not falling within the scope of Regulation (EC) No 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin (EMA/CVMP/519714/2009-Rev.1) the CVMP concluded that the consumption of products derived from animals vaccinated with Proteq West Nile presents no risk for human health. Consequently, the withdrawal period is set at zero days.

Efficacy assessment

West Nile virus (WNV) is a mosquito-borne *Flavivirus* of the Japanese encephalitis virus complex, responsible for a potentially fatal or debilitating disease in horses and humans. The infection is well known in Africa, Asia, the Mediterranean basin and the United States. Several outbreaks have occurred in Europe since 2000.

The primary transmission cycle of WNV involves birds and mosquitoes. Horses become infected through the bite of infected mosquitoes and develop a WNV viraemia of low magnitude and short duration. Therefore, infected horses are unlikely to serve as amplifying hosts for WNV and are considered incidental, dead-end hosts.

West Nile Virus is a neuropathogenic virus causing disease in birds, horses and humans. Symptoms in horses are rare but severe once present. Equids appear to develop clinical signs of WNV infection, including fatal encephalitis, more readily than do other domestic mammals, with the most common clinical signs in equids being weakness, incoordination, and ataxia. However, not all infected horses will develop clinical symptoms: only a maximum of 10% of horses infected with WNV will exhibit neurological symptoms, with a fatality rate in case of clinical disease of 25-40%.

West Nile disease can become a potential threat to horses in some European regions, with only supportive symptomatic treatment once clinical signs appear. Prevention against West Nile disease through vaccination will greatly reduce the number of clinical outbreaks.

The claims of the vaccine are:

For active immunisation of horses from 5 months of age or older against West Nile disease by reducing the number of viraemic horses. If clinical signs are present, their duration and severity are reduced.

Onset of immunity: 4 weeks after the first dose of the primary vaccination course. In order to achieve full protection the full vaccination course of two doses must be given.

Duration of immunity: 1 year after a full primary vaccination course of two injections.

The vaccine schedule is as follows:

Administer one dose (1 ml), by intramuscular injection, preferably in the neck region, according to the following schedule:

Primary vaccination course: first injection from 5 months of age, second injection 4-6 weeks later,

Revaccination: annual booster injections.

In order to demonstrate the efficacy of the Proteq West Nile vaccine, several studies, using both challenge with WNV and serological follow-up, were carried out in the target animal species, equines, with unvaccinated animals as controls. In all the studies, the vaccine was administered via the recommended route, i.e. intramuscularly, and the antigen content tested was the minimum quantity claimed for the vaccine, i.e. 6.0 $\log_{10}$ $CCID_{50}$, or less.

The vaccine used in some of the efficacy studies is the vaccine Recombitek Equine West Nile Virus which is registered in North America and has the same composition as Proteq West Nile but this vaccine has a freeze dried presentation. Notwithstanding this different presentation, the CVMP concluded on the data provided that these two vaccines are similar enough to allow conclusions to be drawn for Proteq West Nile from the Recombitek Equine West Nile virus data.

Since clinical symptoms due to West Nile disease are rare in horses, efficacy under field conditions is very difficult to demonstrate, as the number of horses to be included would need to be very high. As a consequence, no studies were conducted in the field to assess efficacy of the product. However two different and effective challenge models were developed and used in the laboratory to reproduce the disease.

Some of the efficacy studies were performed with the vaccine Recombitek Equine West Nile Virus registered in the USA. The US vaccine is constituted of two vials, one containing the freeze-dried pellet of vCP2017 active ingredient and the other one containing the liquid diluent of carbomer adjuvant. The EU vaccine is ready to use, for an improved convenience for the end user.

The change of pharmaceutical form of Proteq Flu and Proteq Flu-Te vaccines, from the freeze-dried to the liquid formulation was considered acceptable. This modification was shown to have no impact on safety and efficacy of Proteq Flu and Proteq Flu-Te, and it is reasonably assumed that it is also the case for Recombitek West Nile versus Proteq West Nile.

The vaccine Recombitek Equine West Nile was produced in the US facilities. The vaccine Proteq West Nile is produced in France by MERIAL. The applicant demonstrated that the vaccines produced on both sites are equivalent.

In order to demonstrate the efficacy of the Proteq West Nile vaccine, nine laboratory studies, using both challenge with WNV strains from lineage 1 and from lineage 2, and serological follow-up, were carried out in the target animal species with unvaccinated animals as controls. In all the studies, the vaccine was administered via the recommended route (intramuscular), and the antigen content tested was the minimum quantity claimed for the vaccine, *i.e.* 6.0 $\log_{10}$ $CCID_{50}$, or less. In one laboratory study performed with Recombitek Equine West Nile, the vaccine used contained the maximum protective dose (7.8 $\log_{10}$ $CCID_{50}$).

The vaccines used in the studies were either the vaccine Recombitek Equine West Nile registered in North America that has the same composition as Proteq West Nile (except this vaccine has a freeze dried presentation) or the Proteq West Nile vaccine. The relevance of the Recombitek Equine West Nile vaccine with regard to Proteq West Nile was demonstrated by the applicant.

In the different studies a high proportion of vaccinated horses did not develop viraemia when compared to controls. Nevertheless as in some studies, some vaccinates presented viraemia, the following claim was granted: For active immunisation of horses from 5 months of age or older against West Nile disease by reducing the number of viraemic horses.

With regard to clinical signs, after a challenge using the model with WNV infected mosquitoes no clinical signs were observed in vaccinates or controls. After a severe challenge (intrathecal administration), in some studies, the protection against clinical signs is not complete and some vaccinates exhibit clinical signs even if these were considerably milder and of shorter duration than for controls. The following claim was granted: if clinical signs are present, their duration and severity are reduced.

Duration of immunity

The applicant claims that an annual booster injection is sufficient for the revaccination. A study was provided which shows that a single booster injection induces an anamnestic serological response similar to the response observed after the two injections of primary vaccination. The reliability of this study is questionable. Furthermore, the applicant did not provide any demonstration that there is relationship between the antibody response measured and the degree of protection against WNV

infection or disease. Therefore the argument to support a booster injection with a single dose seems weak.

On the other side, the applicant has provided an efficacy study against an experimental WNV-infected mosquito challenge in horses performed with a single dose of vaccine. The results show that there is a reduction of the number of viraemic horses in the vaccinated group compared to the controls. The protection against viraemia was observed even in the absence of detectable WNV serum antibodies at the time of challenge.

For all the centrally authorised vaccines containing the canarypox vector (Proteq Flu range, Purevax Rabies, Purevax Felv and the derivatives), the SPC mentions in section 4.9 that the revaccination is annual.

Taking into account these different points and considering that Proteq West Nile is a MUMS/Limited Market product, no additional trials or data will be required. It was agreed to have an appropriate wording to reflect this in the SPC.

In conclusion, the efficacy of Proteq West Nile has been shown to be acceptable.

Benefit risk assessment

Proteq West Nile is a live recombinant canarypox virus that expresses the genes preM/E of the West Nile virus. It is presented as a suspension for injection that contains carbomer (4 mg/dose) as adjuvant.

The vaccine is intended for immunisation of horses against West Nile disease by reducing the number of viraemic horses. If clinical signs are present their duration and severity are reduced. The vaccination schedule recommends an intramuscular injection of a first dose of 1 ml from the age of 5 months. Four to six weeks later, a second dose of 1 ml has to be injected. An annual booster vaccination is recommended.

Benefit assessment

The safety and efficacy of Proteq West Nile have been demonstrated in well conducted trials that fulfil the requirements of Directive 2001/82/EC, as amended.

Direct therapeutic benefit

Well-conducted placebo-controlled clinical studies demonstrated that vaccination of horses reduces the number of viraemic horses and horses with clinical signs and prevents the mortality associated with West Nile disease in the case of a severe challenge.

Additional benefits

As a consequence of reduction of viraemic horses, the incidence of clinical outbreaks should also be reduced.

Risk assessment

The risk using this vaccine can be classified as low.

Main potential risks:

- for the target animal: there are mild and transitory local reactions at the injection site, resolving within few days and a transiently elevated body temperature within acceptable limits.
- for the user: accidental self-injection is the only identified risk and the standard appropriate warning has been included in the SPC to mitigate that risk.

- for the environment: negligible risk identified from the use of this vaccine
- for the consumer: no specific risk for the consumer of meat from vaccinated animals has been identified.

Risk management or mitigation measures

The SPC contains appropriate warnings in the relevant sections.

Evaluation of the benefit risk balance

The product is well tolerated by the target animals and presents a low risk for users and the environment. West Nile disease can become a potential threat to horses in some European regions, with only supportive treatment once clinical signs appear. Prevention against West Nile disease through vaccination will greatly reduce the number of clinical outbreaks while the vaccine is considered safe when used in compliance with the SPC.

Conclusion on benefit risk balance

The risks linked to the use of this vaccine are considered low. Vaccination reduces the number of viraemic horses. If clinical signs are present their duration and severity are reduced. Consequently, the benefit-risk assessment is favourable for this vaccine, within the limits highlighted in the SPC.

Conclusion

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