Paul-Ehrlich-Institut

Beurteilungsbericht zur Veröffentlichung

(gemäß § 31 Abs. 2 Tierimpfstoff-Verordnung)

chevipok

Antrag für " immunological veterinary medicinal products intended for minor use or minor species/limited markets (MUMS)"

Zulassungsdatum:	20.06.2011
Zulassungsnummer:	PEI.V.11530.01.1
Datum der Erstellung des öffentlichen Beurteilungsberichts:	08.07.2011
Datum der Bekanntgabe beim Antragsteller der/des Zulassungsänderung/Widerrufs, Rücknahme, Anordnung des Ruhens der Zulassung:	

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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

chevipok

MODULE 1

PRODUCT SUMMARY

EU Procedure number	n.a.
Name, strength and pharmaceutical form	Chevipok lyophilisate and diluent for suspension for pigeons
Applicant	chevita GmbH Raiffeisenstraße 2 85276 Pfaffenhofen
Active substance(s)	Live pox virus
ATC Vetcode	QI 01 ED 01
Target species	pigeon
Indication for use	Pox vaccine

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Veterinary Medicines Agencies website (http://www.HMA.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	§ 20 Tierimpfstoff-Verordnung vom 24. Oktober 2006 (BGBl. S. 2355)
Date of completion of the original <mutual recognition> <decentralised>procedure	n.a.
Date product first authorised in the Reference Member State (MRP only)	n.a.
Concerned Member States for original procedure	n.a.

I. SCIENTIFIC OVERVIEW

Chevipok is a lyophilised live viral vaccine with diluent for suspension. It contains live pigeon pox virus, strain NJ. The vaccine is used for active immunisation of pigeons against pigeon pox from the age of 4 weeks onwards. The active immunisation of pigeons reduces the clinical symptoms and the severity of the lesions caused by pigeon pox virus.

One dose consists of 0.1 ml administrated through feather follicle route, for subcutaneous injection one dose of vaccine consists of 0.2 ml. The immunity starts at the latest 21 days after vaccination and provides protection for at least 9 months. The withdrawal period is zero days.

The product sizes marketed are 1 vial containing 50 doses and 1 vial of 10 ml diluent, 2 vials containing each 50 doses and 2 vials of 10 ml diluent, and 1 vial containing 100 doses and 1 vials of 20 ml diluent.

The proposed shelf life is 15 months for the vaccine and 36 months for the diluent. The proposed shelf life after reconstitution is 2 hours.

The vaccine should be stored between +2°C and +8°C and it should not be frozen.

The quality, safety and efficacy of the vaccine complies with all relevant legal provisions.

The results from the safety and efficacy trials are reflected in the SPC.

The vaccine therefore has a positive benefit-risk-ratio.

II. QUALITY ASPECTS

A. Composition

The product consists of lyophisate and diluent for suspension.

The lyophilisate contains Pigeon poxvirus strain NJ (min. 10^4 EID_{50}*; max. 10^6 EID_{50}* (*EID_{50} = egg-infectious-dose: the titre which is needed to cause infection in 50% of embryos after application of vaccine virus), Buffer solution and stabilizer.

The diluent contains di-sodium phosphate dodecahydrate, potassium dihydrogen phosphate, sodium chloride, potassium chloride and water for injection.

The container consists of neutral borosilicate glass bottle, type I hydrolytic glass, Ph. Eur. 30201. The vaccine containers are closed with chlorobutyl rubber stoppers and the diluent containers with bromobutyl rubber stoppers (type I, Ph. Eur. 30209). For protection of vials with lyophilised vaccine total aluminium tear-off caps are used, for protection of vials with diluent central aluminium tear-off seals are used.

The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the vaccine strain as well as the formulation of vaccine and diluent formulation are justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

The active substance is Pigeon poxvirus strain NJ, an established active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur 2.6.24; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production (immunologicals)

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. The tests include in particular Content of Virus, Identity, Residual humidity, Sterility, Appearance, Safety, Mycoplasma, Extraneous agents (PCR) and Extraneous agents (Serology).

The demonstration of the batch to batch consistency is based on the results of 4 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

III. SAFETY ASSESSMENT

The vaccine virus used in the safety studies is working seed virus (WSV) and commercial vaccine batches, produced and tested as described in Part 2 of this dossier.

Laboratory trials

Chevipok as a pigeon pox vaccine belongs to immunological veterinary medicinal products intended for minor use or minor species/limited markets (MUMS). According to the "Guideline on data requirements of IVMPs intended for minor use or minor species/limited markets" EMA/CVMP/IWP/123243/2006-Rev.2 (MUMS guideline), there is a reduced requirement of data asked for in these licensing procedures than in the case of regularly licensed products.

The safety of the administration of one dose (performed with WSV, maximum dose 10^6 EID_{50}), an overdose and the repeated administration of one dose (combined study, allowed by MUMS guideline, performed with commercial batch) in the target animal is demonstrated in studies using 11 (administration of one dose) or 20 (overdose and the repeated administration of one dose) animals of the minimum age for vaccination (4 weeks) for each route of administration (subcutaneous (sc) and via feather follicle (ff)). A control group of non-vaccinated animals is included in each trial. The animals were observed for clinical signs for a period of 21 days. All vaccinated animals and the unvaccinated controls in all studies remained clinically healthy. No adverse systemic reaction was recorded and none of the pigeons died. Milder local reactions were observed which are typical for pox vaccination.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. In case of the overdose and repeated administration of one dose study, the used doses ($10^{6,8}$ EID_{50} and $10^{5,8}$ EID_{50} were slightly under the maximum dose/10fold maximum dose which is allowed according to the MUMS guideline, where the min/max requirement not necessarily has to be proven.

Overdose and repeated application do not induce clinical signs. The vaccine does not spread significantly to unvaccinated contact birds. No relevant residues in food producing animals are expected. Harm to the environment or to human or animal health is not expected. No investigation of effect on reproductive performance was conducted. This again is in line with MUMS guideline.

(Omission of studies of the effect on reproduction or the immune systems will be accepted. If not performed, relevant warnings should be given in the SPC)

This is considered in the SPC:

4.7: The safety of the veterinary medicinal product has not been established during lay. It is therefore recommended to use the vaccines during the lay only accordingly to the benefit / risk assessment by the responsible veterinarian.

There were also no studies performed to examine whether the vaccine affects the immune system of the vaccinated animal or its progeny. The vaccine is not foreseen to be used in association with other vaccines. A corresponding warning is included in the SPC:

4.8: No information is available on the compatibility of this vaccine with any other. Therefore the safety and efficacy of this product when used with any other (either used on the same day or at different times) has not been demonstrated.

6.2: Do not mix with any other medicinal product.

Specific studies were carried out to describe the spread and reversion to virulence of the vaccine strain. The applicant demonstrates that there is no statistical significant increase in virulence between the WSV and the 5th passage. The spread from vaccinated animals to unvaccinated contact pigeons is regarded as very limited. For dissemination, a detailed statement is given by the applicant based on literature and an analysis of the data obtained from the other safety studies. The safety tests performed show no evidence that the virus induces lesions in inner organs, therefore no significant dissemination in the body is expected up to the current knowledge. Also for recombination or genomic reassortment of strains, user safety and study of residues a statement is given by the applicant. The risk of recombination or genomic reassortment is considered to be at theoretical level. No evidence is seen that the avian pox virus can infect humans. Considering the results of the safety tests, contact pigeons do not take or multiply the vaccine virus in significant amounts which lead to clinical signs. The only ingredient relevant for a residue calculation is enrofloxacin. The maximum quantity administered per pigeon will be 12ng, which is far below the 100µg/kg specified for poultry.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

4.8: No information is available on the compatibility of this vaccine with any other. Therefore the safety and efficacy of this product when used with any other (either used on the same day or at different times) has not been demonstrated.

Field studies

A field study was performed using 620 racing pigeons, from 10 weeks to 5 years of age which were vaccinated with one dose ($10^{5,5}$ EID_{50}) of a commercial batch of chevipok either by ff (150) or sc (470) route. The animals were vaccinated against PMV1 and herpesvirus 2-4 weeks before the pox vaccination. The animals were observed for clinical signs for a period of 21 days after vaccination against pox. No clinical signs in the vaccinated pigeons were observed. 12.9% of the animals vaccinated by ff method developed milder local reactions, which is the case for about 55% of the animals vaccinated by sc route. All local reactions /lesions were in the stadium of regression or totally healed at the end of the observation period.

The field trial gives a good analysis of the safety of the vaccine under field conditions. The data confirm the results of the laboratory trials.

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that the composition and safety profile of the product allow regarding the vaccine as safe and that no further studies are necessary.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Based on the composition and the safety profile of the product as demonstrated in the safety and efficacy studies, no risk for the environment, human and animal health is expected.

IV. EFFICACY

IV.B Laboratory Trials

The vaccine batches used in the efficacy studies are commercial vaccine batches, produced and tested as described in Part 2 of this dossier.

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine is efficacious when applied according to the instructions.

To decide about the best time for vaccination, 38 pigeons (28 MDA+ and 10 MDA-) were vaccinated with one dose 9 weeks prior to lay. The decline of antibodies was measured at 2, 3 and 4 weeks of age. As no antibodies were

detectable after 4 weeks, this time point is set as the recommended age for vaccination.

To determine onset and duration of immunity, challenges were performed by ff route at 3 weeks in vaccinated pigeons (23 pigeons vaccinated by ff, 23 by sc route) ,9 months (20 ff, 20 sc) and 13 months (15 ff, 10 sc) after vaccination. At least 10 not vaccinated controls were included in each study. The animals were observed for 21 days after challenge in each trial.

None of the vaccinated animals developed clinical signs and no animal died at any time of challenge. A small amount of animals showed lesions of the follicles after challenge. All controls developed severe clinical signs and/or large lesions and crusts.

The protection rate at 3 months of challenge is calculated with 99,7% for ff and 99,6% for sc application, at 9 months of challenge with 96,6% for ff and 98,3% for sc application and at 13 months of challenge with 62,99% for ff and 71,06% for sc application.
The onset of immunity is determined with 3 weeks after vaccination and the duration with 9 months accordingly.

Field Trials

A field study was performed using 620 racing pigeons, from 10 weeks to 5 years of age were vaccinated with one dose ($10^{5,5}$ EID_{50}) of a commercial batch of chevipok either by ff (150) or sc (470) route. The animals were vaccinated against PMV1 and herpesvirus 2-4 weeks before the pox vaccination.

A challenge was performed on 30 vaccinated (15ff/15sc) and 5 unvaccinated pigeons 21 days p.vacc., and the animals observed for 21 days after challenge.

The challenge did not induce clinical signs in the vaccinated animals. Only 1 pigeon of each vaccinated group developed slight irritations at the follicles where the challenge virus was applied.

All control birds developed degree 4 lesions from the 7^{th} day p.ch. onwards.

The results of the field study confirm the efficacy proven in the laboratory trials. No negative impact from other vaccinations administered 2-4 weeks before the pox vaccination was observed.

V . OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.