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SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Vectormune FP ILT + AE (EMEA/V/C/005077/0000)

Vaccine common name: Fowlpox, avian infectious laryngotracheitis vaccine (live, recombinant) and avian encephalomyelitis vaccine (live)

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

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Introduction

The applicant Ceva-Phylaxia Co. Ltd submitted on 28 November 2018 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Vectormune FP ILT + AE, through the centralised procedure under Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 25 May 2018 as Vectormune FP ILT + AE has been developed by recombinant DNA technology.

Vectormune FP ILT + AE is a live, genetically modified organism (GMO), virus vaccine consisting of a recombinant fowlpox virus (FPV) expressing the membrane fusion protein and the encapsidation protein of avian infectious laryngotracheitis virus (ILTV) and avian encephalomyelitis virus (AEV), strain Calnek 1143.

The product is intended for the following indications: For active immunisation of chickens of 8 to 13 weeks of age in order to reduce the skin lesions due to fowlpox, to reduce the clinical signs and tracheal lesions due to avian infectious laryngotracheitis and to prevent egg production losses due to avian encephalomyelitis. The product is to be applied by wing web administration with the help of a pronged applicator.

Onset of immunity:

Fowlpox and avian infectious laryngotracheitis: 3 weeks after vaccination

Avian encephalomyelitis: 20 weeks after vaccination

Duration of immunity:

Fowlpox: 34 weeks after vaccination

Avian infectious laryngotracheitis and avian encephalomyelitis: 57 weeks after vaccination.

Vectormune FP ILT + AE is presented in glass vials containing 1000 or 2000 doses of vaccine. The solvent is presented in glass vials containing 10 ml (1000 doses) or 20 ml (2000 doses). The packs contain the pronged applicator.

The rapporteur appointed was Jacqueline Poot and the co-rapporteur was Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

On 20 February 2020, the CVMP adopted an opinion and CVMP assessment report.

On 24 April 2020, the European Commission adopted a Commission Decision granting the marketing authorisation for Vectormune FP ILT + AE.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A detailed description of the pharmacovigilance system (dated June 2017, DDPS.PHV.16.2017.06) which fulfils the requirements of Directive 2001/82/EC was provided. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the final product takes place at Ceva-Phylaxia, Budapest, Hungary. The site has a manufacturing authorisation issued by the National Food Chain Safety Office of Hungary. Good Manufacturing Practice (GMP) certification, which confirms the date of the last inspection and shows that the site is authorised for the manufacture and batch release of such veterinary dosage forms, has been provided.

Secondary packaging and batch release take place at the Ceva-Phylaxia site in Budapest as well as at Ceva Santé Animale, Libourne, France which holds a manufacturing authorisation issued by Agence Nationale du Médicament Vétérinaire. GMP compliance was confirmed by the competent national authority.

A GMP declaration for the active substance(s) manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an audit by the manufacturing site responsible for batch release which has taken into consideration the GMP certificate available for the active substance site issued by the National Food Chain Safety Office of Hungary, following inspection.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of the active substances and of the finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 – Quality

Chemical, pharmaceutical and biological/microbiological information (quality)

Qualitative and quantitative particulars of the constituents

Qualitative and quantitative particulars

The active ingredients in the vaccine are a live recombinant FPV vaccine strain, expressing the gB and UL-32 genes of ILTV and a live Avian Encephalomyelitis (AE) conventional vaccine strain.

The stabiliser contains sucrose, lactose monohydrate, sorbitol, gelatin, tryptose phosphate broth, potassium dihydrogen phosphate, dipotassium phosphate and water for injections. The solvent consists of water for injections, glycerol and patent blue V (E131).

The pharmaceutical form is a lyophilisate for suspension for wing web injection after reconstitution in sterile vaccine solvent. The inoculation volume is 0.01 ml.

Container and closure

The lyophilisate and the solvent are filled in hydrolytic resistance type I colourless glass vials. The closure for the different vial sizes consists of bromobutyl rubber stoppers. The vials are sealed by aluminium/plastic tear-off caps.

The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate. The glass vials are sterilised in accordance with European Pharmacopoeia (Ph. Eur.) 5.1.1 requirements.

Product development

The FP parent strain (vector virus) is widely used and has a good safety profile. Two ILTV genes were inserted in the FP vector; the gB gene, derived from a US field strain, and the UL-32 gene, derived from a Japanese field strain. The AE component is the well-known Calnek 1143 strain that is widely used as a vaccine strain.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. The stabiliser components were chosen to provide protection for the viruses during freeze-drying and stability during the shelf life. The solvent contains glycerol for increased viscosity, which aids the wing web vaccination method, and patent blue V which is a dye that acts as an aid to monitor vaccination.

The formulation of batches used during clinical studies was the same as that intended for marketing.

Description of the manufacturing method

The manufacturing process consists of three main steps: the production of the rFP-LT and AE viruses and the production of the finished product.

The rFP-LT virus production consists of preparation of CEF monolayers from SPF embryonated eggs, followed by inoculation with rFP-LT working seed virus. After harvest, the virus suspension may be stored frozen.

For AE virus production consists of SPF eggs inoculated with AE WSV, then incubated. At the end of incubation period, all eggs are cooled, and egg material is harvested and homogenised. The suspension may be stored frozen.

The finished product is blended to achieve a target titre for both viruses. The final composition is composed of the active substances and a stabiliser solution. After filling, vials are freeze-dried. After freeze-drying, vials are capped and stored at 2-8 °C until distribution.

The components of the solvent are mixed. The bulk solvent is autoclaved before filling.

The manufacturing process for the freeze-dried vaccine has been validated. It has generally been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process control tests are adequate for this type of manufacturing process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Starting materials listed in pharmacopoeias are compliant with relevant pharmacopoeial monographs.

The nature of the raw materials, controls and treatments applied minimise the risk of introduction of any extraneous agent to effectively zero.

Specific materials not listed in a pharmacopoeia

Starting materials of biological origin

Genetic engineering: the cloning and construction process is described in detail. Standardised methods were used. The stability of rFP-LT Master Seed Virus has been shown.

The information provided is in accordance with the Guideline on live recombinant vector vaccines for veterinary use.

The two MSVs were tested in accordance with relevant Ph. Eur. monographs.

Other starting materials of animal origin:

A TSE risk assessment in accordance with the note for guidance is provided. The conclusion that the risk for transmission of TSE with this product is negligible can be supported. The applicant has provided an extraneous agents risk assessment. Materials of animal origin, including the master seeds, have been assessed. The conclusion that the risk for transmission of extraneous agents with this product is negligible is supported.

Starting materials of non-biological origin

A CoA has been provided for patent blue V (E131), which conforms to in-house specifications and illustrates compliance with EU Regulation 231/2012.

In-house preparation of media and solutions consisting of several components

Information regarding the qualitative and quantitative composition of all culture media and the stabiliser, their sterilisation and their storage conditions is provided in the dossier.

Control tests during the manufacturing process

Flow charts of the production process of freeze-dried vaccine and solvent are presented that indicate the in-process controls. These include control parameters that are monitored during production and later the following control tests: titration and sterility of the active ingredients and filled volume (for vaccine and solvent).
Test descriptions and the limits of acceptance were presented. The relevant test methods for in-process controls are satisfactorily validated. The in-process tests are deemed to be sufficient to control all the critical steps in the manufacturing.

Control tests on the finished product

The finished product is tested for appearance, identity, potency (virus titration), sterility, absence of mycoplasmas, absence of extraneous agents and residual humidity. The solvent is tested for

appearance, pH, viscosity and sterility.

Identity of rFP-LT virus is performed by immunostaining of infected cells. Absence of mycoplasmas and of specific extraneous agents is tested by PCR; a general test is not included.

The description of the methods used for the control of the finished product and the specifications were provided. Methods are appropriately validated and in accordance with respective Ph. Eur. monograph requirements. The applicant has justified the absence of general tests for extraneous agents based on an assessment of risks and the confirmation of SPF status of the hen's eggs at least 5 weeks after the last laying date (in compliance with Draft Ph. Eur. 5.2.5 (07/2020).

Batch-to-batch consistency

Manufacturing details and results of in-process and finished product testing of four consecutive batches of freeze-dried vaccine have been summarised. The batches conformed to the requirements for the in-process and finished product testing.

Manufacturing details and test results of three consecutive pilot batches of solvent are summarised in tabular format. The batches conformed to the requirements for in-process and finished product testing.

The data provided support the establishment of the manufacturing process and the control tests.

Stability

Data on the stability of the bulk active ingredients were provided. The bulk antigens can be stored for 15 months at -20 °C. Real-time stability data of four batches of finished product for 24 months at 2-8 ºC showed no loss in titre for rFP-LT over this period. For the AE component, the estimated titre loss over 24 months is 0.34 log10 EID50/dose. An overage is set for the AE component that is expected to sufficiently cover estimated losses. The proposed shelf life of 21 months is therefore considered adequately supported by the data.

Furthermore, an in-use shelf life of 2 hours after reconstitution is sufficiently demonstrated.

Three batches of solvent were tested for real-time stability. Full results up to 36 months are presented. All followed parameters remained within specifications. The data provided were sufficient to support the proposed 36-month shelf life for the two presentations of the solvent.

Overall conclusions on quality

The information provided on the qualitative and quantitative composition is acceptable. The manufacturing methods for both virus strains can be considered standard for this type of vaccine and are adequately described.

Starting materials listed in a pharmacopoeia are of satisfactory quality.

The procedures implemented to ensure the absence of extraneous agents in starting materials of animal origin are satisfactory. An extraneous agent risk assessment was performed. A TSE risk assessment was performed. The risk that the final product may transmit TSE to the target animal is negligible.

The production method, including in-process controls and quality control on the finished product together with control of the starting materials, ensure a consistent quality of batches of vaccine. The whole production process was satisfactorily evaluated at production scale.

Results of the stability test for the final product show adequate stability during a 24-month storage period at 2-8 °C. The estimated loss in titre for AE is considered to be adequately compensated for by the formulation overage and data are considered to support the proposed 21-month shelf life.

Stability data of reconstituted product show that the vaccine remains stable at room temperature for 2 hours, therefore the proposed 2 hours in-use shelf life can be accepted.

The solvent was shown to be stable for 36 months.

In conclusion, the production process is adequately described and controls in place are appropriate to ensure the quality of the product at release and throughout the shelf life.

The applicant is committing to provide as a follow up measure results for the first 3 commercial batches to be produced for the freeze-dried product and solvent.

Part 3 – Safety

Introduction and general requirements

Vectormune FP ILT + AE is a live vaccine intended for active immunisation of chickens to reduce skin lesions due to FP, to reduce clinical signs and tracheal lesions due to ILT and to prevent egg production losses due to AE. The recombinant rFP-LT virus is a genetically modified organism, the AE vaccine virus is a well-known vaccine strain. A full safety file in accordance with Article 12(3)(j) has been provided.

Safety documentation

Safety studies were conducted to investigate the safety of the product and included 13 laboratory studies and 3 field trials. To investigate the safety of the administration of a tenfold overdose, the vaccine was administered by the wing web route, as recommended. The overdose safety study was reported to be Good Laboratory Practice (GLP) compliant and carried out in target animals of the minimum age recommended for vaccination, using production batches containing 5.4 log10 TCID50 FP-LT and 5.28 log10 EID50 AE per dose. Production batches were used in the field trials.

Studies applicable to live vaccines and GMO products were conducted to investigate the dissemination of a single dose of the vaccine strain, the spread from vaccinated animals to non-vaccinated contacts and reversion to virulence.

Study title
Overdose safety test of Vectormune FP-LT+AE vaccine in SPF pullets
Spreading between animals of wing web administered rFP-LT MSV in SPF chickens
Spreading between animals of wing-web administered AE MSV in SPF chickens
Dissemination in animal of wing web administered rFP-LT MSV in SPF chickens
Dissemination in animal of wing-web administered AE MSV in SPF chickens
Reversion to virulence and overdose (10x) safety of wing-web administered rFP-LT MSV in SPF chickens
Reversion to virulence and overdose (10x) safety of wing web administered AE MSV in SPF chickens
Foreign species overdose safety and spread of Vectormune FP LT vaccine in turkeys

Foreign species overdose safety and spread of Vectormune FP LT vaccine in ducks
Foreign species overdose safety and spread of Vectormune FP LT vaccine in quails
Foreign species overdose safety and spread of Vectormune FP LT vaccine in guinea-fowls
Foreign species overdose safety and spread of Vectormune FP LT vaccine in pheasant
Foreign species overdose safety and spread of Vectormune FP LT vaccine in pigeon
Field safety and efficacy of V057 vaccine in layer chickens in Hungary
Field safety and efficacy of V057 vaccine in layer chickens
Field safety of a live vector vaccine Vectormune FP-LT+AE in commercial layers

Laboratory tests

Vaccine batches used in safety studies were manufactured according to the method described in Part 2 of the marketing authorisation dossier.

For evaluation of the dissemination, spread and increase in virulence studies, FPV and AEV PCR tests were used. Validation for these tests is provided.

Safety of the administration of one dose

The safety of the administration of one dose has not been tested. This is considered justified since the safety of a tenfold overdose was tested.

Safety of one administration of an overdose

One pivotal study and two supportive overdose laboratory studies were provided.

The pivotal study was compliant with GLP standards. An overdose containing 5.4 log10 TCID50 FP-LT and 5.28 log10 EID50 AE per dose, which equals 7.9 times the recommended dose for rFP-LT and 6.0 times the recommended dose for AE, was administered by the wing web route which is the recommended route in the recommended species chickens. Animals were of the minimum age as required.

General observations were performed after vaccination. Clinical signs were monitored daily from Day 0 to Day 21. Body weights were recorded regularly. The injection site was also regularly inspected, including post-mortem macroscopic and microscopic examinations. Tissue samples were tested for presence of AE by PCR.

No clinical signs or mortality were observed in any of the birds. Local reactions indicative of vaccine take (blue dye and scab) were observed in all vaccinates on Day 7; no further reactions were observed later. All vaccinated birds sampled at Day 7 and 41% of birds sampled on Day 21 showed lymphocytic infiltration at the injection site. The mean body weight gain (BWG: D0-D21) of the vaccinates and controls was not significantly different. PCR for AE virus was positive in 3/3 pancreas samples on Day 7 and 14, as well as in samples of brain and small intestine taken at Day 14.

In a supportive study, the safety of rFP-LT MSV at 5.5 log10 TCID50 per dose, which equals 10 times the maximum dose for this component, was tested in twenty 5-week old SPF chickens via the wing web route. Monitoring was performed as described for the pivotal overdose study.

No clinical signs were observed in any of the birds, with the exception of signs of vaccine take (scab at

injection site). Body weight gain was not significantly different between vaccinates and controls. No local reactions or pathological changes were observed at necropsy.

In a second supportive study, the safety of AE MSV at 5.5 log10 EID50 per dose, which equals 10 times the maximum dose for this component, was tested in twenty 5-week old SPF chickens via the wing web route. Monitoring was performed as described for the pivotal overdose study.

No clinical signs or local reactions were observed in any of the birds. Body weight gain was not significantly different between vaccinates and controls. No local reactions or pathological changes were observed at necropsy.

On the basis of the results no safety concerns arose following the administration of an overdose containing rFP-LT at 7.9 and AE at 6 times the recommended dose to SPF layer chickens at the youngest recommended age by the wing-web route. The results of the supportive studies indicate that the wing web application of a tenfold overdose of the separate viral components to SPF chickens of below the youngest recommended age was safe.

The combined results do not indicate any safety concerns for the application of a tenfold overdose.

Safety of the repeated administration of one dose

Vectormune FP ILT + AE is intended for single lifetime application. A study of the repeated administration of one dose is therefore not required and was not performed.

Examination of reproductive performance

No reproductive studies were provided as use of the product is restricted to the period between 8 weeks of age until 4 weeks before the onset of lay. Both vaccine viruses were shown to be cleared from vaccinates within 28 days after vaccination and thus before the point of lay. The vaccine is not expected to interfere with the maturation of the reproductive system. Therefore, no studies have been conducted.

A statement is included in section 4.7 of SPC ("Do not use in birds in lay or within 4 weeks before the start of the laying period").

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions. Neither of the viruses is known to be immunosuppressive, from which it is concluded that the attenuated vaccinal strains will have no impact on immunological functions.

Special requirements for live vaccines

Spread of the vaccine strain

The spread of the vaccine strains from vaccinated to unvaccinated animals was investigated in two separate studies in which 5-week old SPF chickens were vaccinated with a single maximum dose of one of the vaccine viruses (MSV) according to the recommended vaccination schedule by the wing web method route and left in contact with unvaccinated sentinels for up to 28 days. The AE vaccine strain was isolated from cloacal samples of 5 sentinels after 7 days of contact. After 28 days of contact, the AE vaccine strain was isolated from brain tissue of three and pancreas of one sentinel. The rFP-LT vaccine strain was not found in any of the tissues sampled from the sentinel birds.

It is concluded that the rFP-LT vaccine virus is unlikely to spread to in-contact unvaccinated animals,

while the AE vaccine virus does spread to unvaccinated in-contact chicken as is known from the field. For rFP-LT virus, studies were carried out to investigate spreading between other non-target species. Groups of turkeys, ducks, quail, guinea fowl, pheasants and pigeons were vaccinated with a tenfold dose of the rFP-LT virus or the parent FP virus via wing web application and put into contact with groups of sentinel animals. There were no safety issues in the vaccinated animals; a low frequency (5%) of spreading was observed in all species tested for the recombinant rFP-LT strain and/or the parent FP strain. The expected frequency of spreading from vaccinated chickens to non-target species is low and is not considered to present a significant risk.

Dissemination in the vaccinated animal

Dissemination of the vaccine strains in vaccinated animals was investigated in two separate studies.

The rFP-LT vaccine strain was isolated from the lung and trachea of 7% of vaccinated animals for 14 days post-vaccination. The site of injection was positive in 100% of animals on Days 2 to 7 and gradually decreased to 0% on Day 28. The AE vaccine strain was isolated from brain, pancreas, small intestine and proventriculus of 57% of animals for 21 days post vaccination.

In conclusion, both virus strains disseminate following vaccination by the recommended route of a single maximum dose of either virus in 5-week old SPF chickens. The rFP-LT virus can therefore be shed from vaccinates for 14 days post vaccination while the AE virus can be shed for 21 days.

Although Vectormune FP ILT + AE is a live vaccine, the active ingredients are non-pathogenic to non-target avian species, and not able to colonise non-target mammalian species including humans. Study results indicate the vaccine strains do not persist at the injection site or in the organs and tissues for longer than 4 weeks.

Reversion to virulence of attenuated vaccines

The reversion to virulence of the vaccine strains was investigated in two separate studies designed in accordance with the requirements of Ph. Eur. 5.2.6 and Ph. Eur. 0442 monographs, respectively.

Sequential passage of rFP-LT vaccine strain through 6 groups of SPF chickens was investigated. The vaccine strain was recovered at all 6 passages. There were no clinical signs of disease observed at any of the passage levels.

Passage 6 was inoculated into 20 SPF chickens to evaluate safety. No abnormalities were found in the animals vaccinated either with material used for the first passage (MSV) or material recovered from the final passage (MSV+5). No clinical abnormalities or macroscopic pathological changes were observed, and body weight gain was not affected either in the group inoculated with material used for the 1st passage or in the group inoculated with virus recovered from the final passage.

Sequential passage of AE vaccine virus through 6 groups of SPF chickens was investigated. The vaccine strain was recovered at all 6 passages. There were no clinical signs of disease observed at any of the passage levels.

Passage 6 was inoculated via wing web route into 20 SPF chickens to evaluate safety. No abnormalities were found in the animals vaccinated either with material used for the first passage (MSV) or material recovered from the final passage (MSV+5). No clinical abnormalities or macroscopic pathological changes were observed, and body weight gain was not affected either in the group inoculated with material used for the 1st passage or in the group inoculated with virus recovered from the final passage.

It is concluded that no reversion to virulence was observed following six passages *in vivo* for either the

rFP-LT or the AE vaccine strain.

Biological properties of the vaccine strain

Both vaccine strains are derived from well-known and worldwide used vaccine strains. The properties of the rFP-LT strain are further detailed in part 3.E.

Recombination or genomic reassortment of the strains

Avian encephalomyelitis virus is a single-stranded RNA virus. Recombination events between the vaccinal Calnek 1143 AE strain and field strains cannot be excluded. However, these have never been reported despite extensive and worldwide use of the vaccine strain.

Fowlpox virus is a double-stranded DNA virus and recombination is theoretically possible. Recombination with RNA viruses (e.g. AE) is highly unlikely, while recombination with ILT viruses (double stranded DNA virus) is also considered unlikely since only two ILT genes are incorporated in the FPV genome.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guidelines EMEA/CVMP/IWP/54533/2006 and EMEA/CVMP/543/03-Rev.1.

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection and dermal and/or oral exposure. The vaccine viruses are not pathogenic for humans and therefore do not pose a risk for the user. The excipients are commonly used in other vaccines and do not pose a risk for the user. As a result of the user safety assessment the following advice to users/warnings for the user are proposed:

"In case of adverse reactions following accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician."

Study of residues

Excipients

The excipients included in the product are commonly used in other vaccines and do not raise any safety concern.

MRLs

The active substances being principles of biological origin intended to produce active immunity are not within the scope of Regulation (EC) No 470/2009.

The excipients, listed in section 6.1 of the SPC are either allowed substances for which table 1 of the annex to Commission Regulation (EU) No 37/2010 indicates that no MRLs are required or are considered as not falling within the scope of Regulation (EC) No 470/2009 when used as in this product.

The two antimicrobials used in the manufacturing process are present at low residual levels in the finished product, which is not considered to constitute a risk to the consumer.

Residue studies are not required.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with other veterinary immunological products and therefore proposes to include a statement in Section 4.8 of the SPC that 'No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case-by-case basis.'

Field studies

Three positive-controlled parallel group design, partly blinded field studies were conducted to evaluate safety and efficacy. Two studies were performed in layer breeder farms in Hungary, whereas the third was performed in a layer farm in Spain. The studies were conducted in accordance with Good Clinical Practice (GCP).

The studies were well designed and conducted and confirmed that the product is safe for use in commercial layer-type pullets. General health investigations were carried out daily for 4 weeks post vaccination. Mortality was recorded. Local reactions (size, duration, nature of lesions at the site of injection) were assessed at Day 14. Body weight was measured weekly until 4 weeks post vaccination.

No clinical signs associated with vaccination were observed, mortality was similar between investigational veterinary product (IVP)-vaccinated and control-vaccinated groups. Local reactions were recorded on Day 14 following vaccination in 5-13% of IVP treated birds. Body weight gain was not significantly different between IVP-vaccinated and control-vaccinated groups.

Outcomes of primary and secondary safety parameters indicate the vaccine was safe when used under field conditions.

Study 1: Field safety and efficacy trial of Vectormune FP ILT + AE vaccine in layer chickens	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions.
Test product	Group 1: IVP: commercial dose of Vectormune FP ILT + AE
Control product/ Placebo	Group 2: CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Outcomes - safety observations	Mortality rate was 0.18% in Group 1 and 0.11% in Group 2. The difference was not statistically significant. Local reactions were observed in 1/20 birds in Group 1 and 0/20 in Group 2. Mean bodyweight was consistently slightly higher in Group 2 compared to Group 1; the difference was however not statistically significant.
Adverse events	Onset of egg laying was slightly delayed in Group 1, which may have been caused by the numerically lower average body weights in Group 1 or by a delay in the use of egg nests. The overall

	performance was the same within a few weeks. It is unlikely to have been caused by the vaccine, since no clinical signs or local reactions were observed, and mortality was low.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate. The use of a comparator product in a field study is acceptable. Outcomes of primary and secondary safety parameters indicate the vaccine was safe when used under field conditions. Local reactions were observed in 5% of IVP-treated animals. The absence of extended evaluation of egg laying is acceptable based on the safety results.

Study 2: Field safety and efficacy trial of Vectormune FP ILT + AE vaccine in layer chickens	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions.
Test product	Group 1: IVP: commercial dose of Vectormune FP ILT + AE
Control product/ Placebo	Group 2: CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Outcomes-Safety observations	Mortality rate after vaccination (Day 0-41) was 0.845% in Group 1 and 0.908% in Group 2; the difference was not statistically significant. No clinical signs of FP or ILT were observed. At 14 days post vaccination, no local reactions were observed. Mean body weight gain was not significantly different between the groups.
Adverse events	No adverse events were observed.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate; the use of a comparator product in a field study is acceptable. Outcomes of primary and secondary safety parameters indicate the vaccine was safe when used under field conditions. Local reactions were not observed in IVP-treated animals. The absence of evaluation of egg laying is acceptable based on the safety results.

Study 3: Field trial of a live vector vaccine Vectormune FP ILT + AE in commercial layers	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions.
Test product	Group 1: IVP: commercial dose of Vectormune FP ILT + AE
Control product/ Placebo	Group 2: CVP 1, CVP 2 and CVP3: Hiprapox, Poulvac ILT and Bio EA

Results	
Outcomes-Safety observations	Local reactions were observed in 13% of birds in Group 1 and in 20% of birds in Group 2. Mean body weight gain as measured in 100 birds per group, weekly between week 9 and 15, was significantly higher in Group 1 compared to Group 2; the difference was 0.032 kg. Higher mortality rate over the rearing period was recorded in Group 1 (3.5%) compared to Group 2 (1.5%); this was mainly due to an aspergillosis outbreak in Group 1 (causing 1.79% of deaths) between week 4 and 7 (prior to vaccination). Post-vaccination mortality was not significantly different between the groups. No clinical signs attributable to the treatments were observed. Because weight gain and clinical signs did not indicate vaccine-related safety issues, egg laying was not evaluated as a safety parameter.
Adverse events	No adverse events were observed.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate; the use of comparator products in a field study is acceptable. Outcomes of primary and secondary safety parameters indicate the vaccine was safe when used under field conditions. Local reactions were observed in 13% of IVP-treated animals at Day 14 post vaccination. The absence of evaluation of egg laying is acceptable based on the safety results.

Environmental risk assessment

A Phase 1 Assessment of environmental risk was performed in accordance with the CVMP note for Guidance (EMEA/CVMP/074/95).

Considerations for the environmental risk assessment

Both AE and FP viruses have the capacity to transmit to non-target (avian) species. AE virus can infect other birds present on a farm, including turkeys, pheasants, pigeons, ducks and quail. Although the rFP-LT vaccine strain was shown not to be shed by vaccinated chickens, the applicant performed safety studies in non-target animals; the vaccine strain was shown to be safe in turkeys, ducks, quails, guinea fowls, pheasants and pigeons. There is no capacity of the live organisms to transmit to non-avian species.

The vaccine viruses cannot multiply in the environment. The vaccine is applied by injection, which precludes its dispersion in the environment. The AE vaccine strain can be shed by vaccinated animals and survive for up to 3 weeks in the environment. The rFP-LT strain was shown not to be shed and survival in the environment is limited.

The components of the product are not toxic. There are no known toxic metabolites.

Based on the data provided, the ERA can stop at Phase I. Vectormune FP ILT + AE is expected to pose a negligible risk to the environment when used as recommended. To limit the spread of AE to susceptible birds, appropriate risk mitigation measures are described in the SPC.

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

Vectormune FP ILT + AE falls within the scope of Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms. Detailed information on the possible risks for humans and for the environment has been provided.

The recombinant FP-LT strain does not infect humans or other mammals.

The vaccine strain was generated by homologous recombination to insert a cassette containing ILT gB and UL-32 genes and *E. coli* LacZ gene, under the control of synthetic consensus poxvirus promotors. The parent FP strain is a well-known commercial vaccine strain; the inserted ILT genes are not known as virulence factors, which minimises the risk for reversion to virulence. Accordingly, reversion to virulence studies (*in vivo* and *in vitro*) did not show any tendency for genetic instability or reversion.

The vaccine virus was not shed from vaccinated animals via secretion or excretion. Commingling of sentinels with vaccinated animals did not lead to infection of the sentinels. Accordingly, no biologically relevant spread of the vaccine viruses into the environment could be detected.

Taken together, any risk emerging from the use of the rFP-LT vaccine virus is expected to be negligible for humans and for the environment.

Overall conclusions on the safety documentation

The applicant has provided one pivotal and two support laboratory studies to investigate the safety of an overdose to target animal species of the minimum recommended age via the recommended wing web route. Batches used in these studies were routine. Repeated administration was not investigated. This is accepted since the vaccine is to be applied as single lifetime injection. No clinical signs or mortality were observed in any of the birds, beside local reactions indicative of vaccine take (small scab).

Reproductive performance was not studied. A warning is included in the SPC. This is considered acceptable, based on the known safety profile of the (parent) vaccine strains.

The product is not expected to adversely affect the immune response of the target animals or of their progeny, and therefore no tests on the immunological functions were carried out.

No evidence of spread of the rFP-LT strain was obtained from the studies in chickens; dissemination was very limited. The AE vaccine strain is shed and able to spread from vaccinated to in-contact chickens. An appropriate warning is included in the SPC.

Studies showed no reversion to virulence of either the rFP-LT virus or the AE virus.

The applicant has sufficiently addressed the biological properties of the vaccine strains and the risk of recombination or genomic reassortment occurring. The risks are considered to be negligible.

The user safety has been adequately addressed and a warning is included in the SPC.

Residue studies are not required. The withdrawal period is set at zero days.

No compatibility of the vaccine with any other veterinary medicinal product is claimed, therefore no studies were performed. An appropriate warning is included in the SPC.

Based on the data provided, the ERA can stop at phase I. Vectormune FP ILT + AE is not expected to pose a risk to the environment when used in accordance with the SPC.

Since the rFP-LT strains is a GMO, information regarding the origins, method of recombination,

stability, biological properties and genomic sequence of the vaccine strain was provided. The rFP-LT strain was shown to be genetically and phenotypically stable. The insertion of the foreign genes did not change the virulence in the target species or other avian species or mammalians. Any risk emerging from the use of the rFP-LT vaccine virus is negligible for humans and the environment.

Three studies were performed investigating the safety of the vaccine when applied under field conditions. Based on evaluation of local reactions, clinical signs, mortality and weight gain, the vaccine was shown to be safe. Potential effects on egg laying were not evaluated; however, adequate justification was provided.

In conclusion, when used as directed, the vaccine is considered to be generally safe for the target animal, the environment, the user and the consumer.

Part 4 – Efficacy

Introduction and general requirements

Vectormune FP ILT + AE is intended for active immunisation of chickens to reduce skin lesions due to FP, to reduce clinical signs and tracheal lesions due to ILT and to prevent egg production losses due to AE.

The vaccine is intended to be administered to layer chickens from 8 to 13 weeks of age. Immunity is intended to be established 3 weeks after a single injection for FP and ILT and 20 weeks after vaccination for AE.

The proposed duration of immunity is 34 weeks for FP and 57 weeks for ILT and AE.

Efficacy was demonstrated in compliance with the European Directive 2001/82/EC (as amended by 2004/28/EC and Directive 2009/9/EC), and the European Pharmacopoeia (Ph. Eur.) chapter 5.2.7.

Challenge model:

The challenge strains used were isolated in Europe or coming from other fully justified sources, based on epidemiological data. For FP, the FP-SBS challenge strain was used. For ILT the challenge strain was sourced from USA. For AE the vaccine strain, Calnek 1143 was used.

The challenge models were adequately justified and shown to be appropriate to mimic the natural conditions for infection.

Efficacy parameters and tests:

The efficacy parameters, as chosen by the applicant, investigated in the efficacy studies are skin lesion scores for FP, general and respiratory clinical signs, mortality and tracheal lesions for ILT and egg production rate for AE. The parameters chosen are considered appropriate for evaluating the claimed efficacy of the product.

Efficacy documentation

22 studies were conducted to investigate the efficacy of the product and included 19 laboratory studies and 3 field trials. Laboratory studies were well documented and carried out in target animals of the minimum age recommended for vaccination, using pilot and production batches.

Study title
Feasibility efficacy study of V057 vaccine challenged with FP strain
Onset of immunity test of the FP part of V057 vaccine in layer chickens
Onset of immunity study of V057 vaccine in SPF chickens challenged with ILT challenge strain.
Onset of immunity test of the ILT part of V057 vaccine in layer chickens
Onset of immunity test of V057 vaccine in commercial layers challenged with Avian Encephalomyelitis virus
Vaccination and vaccine take control of V057 vaccine in SPF chickens
Vaccination and vaccine take control of V057 vaccine in susceptible pullets
Duration of immunity test of the FP part of V057 vaccine in pullets at 56 weeks of age
Duration of immunity test of the FP part of V057 vaccine in SPF chickens at approximately 42 weeks of age
Duration of immunity test of the ILT part of V057 vaccine in SPF chickens at approximately 65 weeks of age
Duration of immunity test of ILT part of V057 vaccine in pullets at the beginning of lay
Duration of immunity test of the ILT part of V057 vaccine in SPF chickens at approximately 30 weeks of age
Duration of immunity test of the ILT part of V057 vaccine in SPF chickens at approximately 50 weeks of age
Duration of immunity test of the ILT part of V057 vaccine in SPF chickens at approximately 51 weeks of age
Duration of immunity tests of the ILT part of V057 vaccine in SPF chickens at approximately 60 weeks of age
Duration of immunity test of V057 vaccine in commercial layers challenged with Avian Encephalomyelitis virus at the end of egg production performance
Duration of immunity test of V057 vaccine in commercial layers challenged with Avian encephalomyelitis virus at the middle of egg production performance
Field safety and efficacy trial of V057 vaccine in layer chickens in Hungary
Complementary FP efficacy test of a layer field trial after wing-web vaccination with V057 vaccine
Complementary ILT efficacy test of a layer field trial after wing-web vaccination with V057 vaccine
Field safety and efficacy trial of V057 vaccine in layer chickens
Field trial of a live vector vaccine Vectormune FP-LT + AE in commercial layers

Laboratory trials

Dose determination

The proposed minimum potency of 2.66 log10 $TCID_{50}$ for the rFP-LT vaccine strain was established based on the findings of a dose determination study. Vaccine doses of 2.66 log10 $TCID_{50}$ and 3.0 log10 $TCID_{50}$ of rFP-LT component were compared. The study was not valid for the high dose group, since 25% of animals died due to reasons not attributable to the vaccination or challenge. In the 2.66 log10 $TCID_{50}$ group, however, all animals were significantly protected from clinical signs of fowlpox.

Onset of immunity

Four studies were performed, three in commercial layer chickens and one in SPF chickens - all at the minimum age of 8 weeks at the time of vaccination - to investigate the onset of immunity, following the recommended administration route.

In an onset of immunity study against FPV, commercial layer pullets were used. In Group 1, 20 commercial layer pullets were vaccinated with a dose of vaccine diluted to contain the minimum amount of rFP-LT component (2.66 log10 $TCID_{50}$ in 0.01 ml); Group 2 consisted of 10 control layer pullets and Group 3 of 10 control SPF birds. After challenge at three weeks with FP strain, animals were observed daily for skin lesions for 3 weeks.

Most of the vaccinated animals showed small fowlpox lesions. Extensive lesions were found in all control animals.

It was concluded that vaccination by the recommended route with a minimum dose of rFP-LT strain was efficacious and met efficacy requirements for FP at 3 weeks post vaccination.

In an onset of immunity study against ILTV, two groups of twenty 8-week old SPF pullets were used. Group 1 was vaccinated with a dose of vaccine diluted to contain the minimum amount of rFP-LT component (2.66 log10 $TCID_{50}$ in 0.01 ml); Group 2 was kept as non-vaccinated controls. All animals were challenged at Day 21 with an intra-tracheal dose of ILTV. Animals were observed daily for general and respiratory clinical signs. All animals were necropsied at 8 days after challenge and tracheal lesions were scored.

Mortality was 0% in Group 1 and 10% in Group 2. Cumulative clinical scores were 1 in Group 1 and 68 in Group 2. Tracheal lesion scores were 0 in Group 1 and 36 in Group 2. These differences were statistically significant.

In conclusion, the vaccine at minimum rFP-LT dose conferred reduction of clinical signs and tracheal lesions due to ILTV in SPF chickens.

Onset of immunity against ILTV was also investigated in commercial layer pullets. Group 1 consisted of twenty 8-week old pullets vaccinated with a dose of vaccine diluted to contain the minimum amount of rFP-LT component (2.66 log10 $TCID_{50}$ in 0.01 ml), Group 2 consisted of 20 control layer pullets and Group 3 of 20 control SPF birds. All animals were challenged at Day 21 with an intra-tracheal dose of ILTV. Animals were observed daily for general and respiratory clinical signs. All animals were necropsied at 8 days after challenge and tracheal lesions were scored.

Mortality was 0% in Group 1, 25% in Group 2 and 25% in Group 3. Cumulative clinical scores were 7 in Group 1, 91 in Group 2 and 137 in Group 3. Cumulative tracheal lesion scores were 5 in Group 1, 67 in Group 2 and 63 in Group 3. These differences were statistically significant.

In conclusion, the vaccine at minimum rFP-LT dose conferred a reduction of clinical signs and tracheal lesions against ILTV in commercial layer pullets.

Onset of immunity study against AEV included three groups of eighty-five 8-week old commercial layer pullets. Groups 1 and 3 were vaccinated with Vectormune FP ILT + AE diluted to contain the minimum dose of AE virus (2.7 log10 EID_{50}/dose of 0.01ml), Group 2 was left unvaccinated. At 28 weeks of age, Groups 1 and 2 were challenged orally with Calnek 1143 strain and Group 3 was left as unchallenged egg production controls. Serum samples were taken on D0, D136 from 30 animals in each group.

MDA was confirmed by serology in 6.7% of birds in Group 1 on Day 0, 0% in Groups 2 and 3. After challenge, egg production rate of Group 2 dropped, whereas it remained high in Groups 1 and 3. The drop in egg production rate was significantly lower in the vaccinated group, compared to the challenge control group and the production rate was not significantly different from that in healthy (unchallenged) birds.

In conclusion, vaccination of commercial layer chicks of the minimum age for vaccination with a minimum dose of the AE component was shown to prevent a drop in egg production due to AE challenge, at 20 weeks post vaccination. This corresponds to the claimed 20-week onset of immunity. A statement indicating that maximum seroconversion was observed between 4 and 7 weeks post vaccination is included in the SPC.

Duration of immunity

Ten studies were carried out in 8-week-old chickens to investigate the duration of immunity by the recommended administration route: two studies investigated immunity to FPV, six for ILTV and two for AEV.

For the studies investigating duration of immunity against FPV and ILTV, SPF chicks were used. In these studies, birds were vaccinated with a batch of vaccine diluted to contain a minimum titre of 2.66 log10 $TCID_{50}$ of the rFP-LT component in 0.01 ml; vaccine take was checked and found to be 100% in both studies.

In a DOI study for fowlpox at 49 weeks after vaccination two groups of ten 8-day old commercial layer pullets were used. Group 1 was vaccinated; Group 2 was unvaccinated. At 49 weeks post vaccination, all animals were challenged with FP-SBS strain. Animals were observed daily for skin lesions for 28 days after challenge. Pox lesions were scored (score 0-5).

The vaccinated birds showed significant skin lesions over the course of the 4-week follow-up period; 90% of birds had score 5 (maximum) on Day 10 and showed gradual improvement (to score 4) thereafter. In the controls, 100% of birds had lesion score 5 from Day 10 until Day 28. Average clinical scores over the follow-up period were significantly lower in the vaccinates.

In conclusion, although a statistically significant difference in severity of pox lesions was observed, it is questioned whether this difference is clinically relevant.

In a DOI study for fowlpox at 34 weeks after vaccination one group of 20 SPF chicks were vaccinated and a second group of 10 animals were kept as controls. All chicks were challenged at 34 weeks post vaccination. Animals were observed daily for skin lesions for 21 days after challenge. Pox lesions were scored (score 0-4).

65% of vaccinates showed notable pox lesions (≥ score 2), 100% of birds in Group 2 had notable pox lesions. The average cumulative lesion score was 24.7 in the vaccinates and 38 in controls; this difference was statistically significant.

In conclusion, the results support a DOI of 34 weeks after vaccination for reduction of pox lesions. A statement is included in the SPC that for fowlpox, increased speed of cicatrisation is observed until 49 weeks after vaccination.

In a DOI study against ILTV at 57 weeks after vaccination one group of 10 vaccinated SPF animals and two groups of controls were used. All animals were challenged intratracheally with a dose of 2.5 log10 EID_{50} of ILTV. Respiratory and general clinical observations were performed daily for one week. At day 8 tracheal lesions were scored.

Mortality was 0% in the vaccinates and 30% in the controls. In both groups 90% of birds showed respiratory signs. Cumulative overall clinical scores were 25 in the vaccinates and 131 in the controls. This difference was statistically significant. Cumulative tracheal lesion scores were 11 in the vaccinates and 31 in the controls. This difference was also statistically significant.

In conclusion, the vaccine at minimum potency for the rFP-LT component is efficacious against ILT challenge, 57 weeks after vaccination of 8-week old SPF chickens.

Five additional studies were performed that investigated the duration of immunity (DOI) against ILTV at 12, 23, 41, 44 and 52 weeks post vaccination. The set-up of these studies was highly similar to the 57-week DOI study described above, albeit the challenge dose varied between 2.8 log10 EID_{50} (12, 23 weeks), 2.5 log10 EID_{50} (41, 52 weeks) and 2.2 log10 EID_{50} (44 weeks). The prevention of mortality and reduction of clinical signs and lesions was confirmed at 12, 23 and 52 weeks. At 41 weeks, prevention of mortality and reduction of tracheal lesions was confirmed, whereas at 44 weeks, reduction of clinical signs was confirmed. The reason for the lack of significant effects on clinical signs at 41 weeks and mortality and tracheal lesions at 44 weeks appears to lie in the lower challenge dose employed at those times, since full protection was achieved at 52 and 57 weeks.

In conclusion, these studies provide further support for the continued immunity against ILTV up to 57 weeks after vaccination.

A DOI study against AEV at 57 weeks after vaccination was performed in three groups of eighty-four to eighty-eight 8-week old commercial layers. Groups 1 and 3 were vaccinated with Vectormune FP ILT + AE diluted to contain 2.7 log10 EID_{50} AE strain. Group 2 was unvaccinated. Groups 1 and 2 were challenged orally with AEV Calnek 1143 strain at 57 weeks post vaccination. Daily individual egg production was recorded.

6.7% of animals in Group 1 were seropositive at Day 0. The difference in egg production after challenge between Group 1 and Group 2 was statistically significant while there was no difference between Groups 1 and 3.

An additional study was set up as described above for the 57-week DOI study, with challenge at 43 weeks post vaccination. The difference in egg production after challenge between Group 1 and Group 2 was statistically significant; there was no notable difference between Groups 1 and 3. This study provides additional support for the continued immunity against AEV up to 57 weeks after vaccination. An overall statistical analysis was performed of the three AEV efficacy studies in commercial layers (OOI at 20 weeks, DOI at 43 weeks p.v. and DOI at 57 weeks p.v.). Based on the combined data, it was concluded that a drop in egg production can be prevented.

Maternally derived antibodies (MDA)

The applicant addressed the issue of efficacy in the presence of MDA by providing literature data concerning the decrease in titre after hatch.

In one study in broilers, antibodies against a range of pathogens (among which AEV and ILTV) were found to be depleted by 10 days of age. In a second study MDA specifically against FPV were found to persist for a maximum of 4 days in chicks derived from vaccinated parents. In studies by Calnek et al, chicks were found to be fully susceptible to AEV at 8-10 weeks of age. In the two AEV DOI studies performed, few birds were found positive at the time of vaccination (2/30).

In the field trial in commercial layers, 10% of animals were AE seropositive at 15 days of age.

Taken together, it can be concluded that MDA is highly unlikely to play a role for FPV or ILTV in birds vaccinated at 8 weeks of age. For AEV, the laboratory (DOI) study supports the efficacy in commercial (MDA+) layer pullets vaccinated at the minimum age of 8 weeks.

Interactions

No compatibility is claimed with any other medicinal product; the standard warning sentence is included in section 4.8 of the SPC.

Field trials

Three positive-controlled combined safety and efficacy GCP field studies were performed, two in Hungary and one in Spain. These studies are also described in part 3 of this report, with respect to the safety parameters.

No outbreaks of FP, ILT or AE occurred during either of the field studies. Therefore, no data on protection against field challenge were obtained. Results showed that in all groups vaccinated with the product the take of the vaccine could be confirmed in 92-100% of animals by development of a small nodule/scab at the injection site. For the AE component, seroconversion occurred and seropositivity levels were similar between the vaccinated and control groups.

In one study, field-vaccinated animals were taken to the laboratory for FPV and ILTV challenges at 23 or 28 weeks of age. Results of these studies indicate that the product, when applied under field conditions, conferred a reduction of clinical signs of FP and reduction of clinical signs and tracheal lesions due to ILTV.

The data generally support the proposed indication for FP and ILTV; since no field challenge occurred, no data on efficacy against AEV were obtained.

Study 1: Field safety and efficacy trial of Vectormune FP ILT + AE vaccine in layer chickens.	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions
Interventions: Vaccine	Commercial dose of Vectormune FP ILT + AE
Control product/ Placebo	CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Efficacy parameter	100% of birds had signs of vaccine take in both groups. After Day 21, 80-100% of birds were AE seropositive in both groups. Seropositivity rate was not found significantly different on any of the sampling days. Complementary FPV challenge: In Group 3 no animals showed notable pox lesions, in Group 1 50% of birds showed notable pox lesions, with a total average score of 45.4. In Group 2, 85% of birds showed notable pox lesions with a total average score of 68.6. The average score in Group 1 was significantly lower than in Group 2.

	Complementary ILTV challenge: mortality was 5% in vaccinates, 20% in controls and SPF controls. Mean total clinical scores were 3 in vaccinates, 5 in controls and 7.5 in SPF controls. The difference between vaccinates and controls was significant. The mean tracheal lesion score was 2.1 in vaccinates, 3 in controls and 3.4 in SPF controls. The lesion score in vaccinates was significantly lower compared to controls.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate. No outbreaks of FP, ILT or AE occurred. The results of the complementary challenges with FPV and ILTV at 23 and 28 weeks p.v., respectively, support the results of the laboratory challenge studies. Prevention of mortality due to ILTV was not achieved in this study. No justification was provided of how the rate of seropositive samples for AE relates to protection.

Study 2: Field safety and efficacy trial of Vectormune vaccine in layer chickens	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions
Interventions: Vaccine	Commercial dose of Vectormune FP ILT + AE, wing web
Control product/ Placebo	CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Efficacy parameter	No outbreaks of FP, ILT or AE occurred. Vaccine take was 100% in both groups. The rate of seropositive samples was not found to differ significantly between vaccinates and controls at any of the time points.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate. The age of the pullets was 12 weeks at the time of IVP vaccination, which is higher than the minimum age for vaccination (8 weeks) but is considered acceptable as it is within the expected age range for vaccination under field conditions. The study results indicate a similar rate of AE seropositive samples for IVP and CVP groups; no justification was provided of how this relates to protection. No data on protection against FP and ILT were obtained.

Study 3: Field trial of a live vector vaccine Vectormune FP ILT + AE in commercial layers	
Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions

Interventions: Vaccine	Group 1: IVP: Commercial dose of Vectormune FP ILT + AE, wing web
Control product/ Placebo	Group 2: CVP 1, CVP 2 and CVP3: Hiprapox, Poulvac ILT and Bio EA
Results	
Efficacy parameters	No outbreak of FP, ILT or AE occurred. Vaccine take was observed in 92/100 birds in Group 1 and 99/99 birds of Group 2. From 4 weeks p.v. the percentage of seropositives was 75±5% in the IVP group and 58±1% in the CVP group.
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate; the use of a comparator product in a field study is acceptable and the study was performed under GCP. Layer pullets were used, which is in accordance with the intended use of the vaccine. The age of the pullets was 12 weeks at the time of IVP vaccination, which is higher than the minimum age for vaccination but can be accepted as it is within the normal age range. The study results indicate a higher rate of AE seropositive samples for the IVP compared to the CVP group; however, no justification was provided on how this relates to protection. No data on protection against FP and ILT were obtained.

Overall conclusion on efficacy

The minimum titre for the rFP-LT component was based on a dose finding study in which a challenge with FPV was performed and reduction of clinical signs was achieved.

Four onset of immunity studies were performed in animals of the youngest recommended age for vaccination (8 weeks) and with vaccine batches containing a minimum titre of either the rFP-LT component (for FP and ILT studies) or the AE component.

Onset of immunity against FPV was shown at three weeks post vaccination by reduction of skin lesions after challenge of commercial layer pullets via the feather follicle route with virulent FP challenge virus.

Two studies were performed for ILTV, one in SPF birds and one in commercial layer pullets. In both studies, onset of immunity was shown at three weeks post vaccination by reduction of clinical signs and reduction of tracheal lesions after challenge with virulent ILT virus via the intratracheal route.

Onset of immunity against AE was shown at 20 weeks post vaccination by prevention of a drop in egg production rate due to oral challenge with high dose Calnek 1143 strain AEV. A statement is included in the SPC indicating that for avian encephalomyelitis maximum seroconversion was observed between 4 and 7 weeks post vaccination.

Duration of immunity was investigated in 10 studies that were performed using 8-week old chickens vaccinated by the recommended administration route: two studies investigated immunity to FPV, six for ILTV and two for AEV.

The duration of immunity against FPV was tested at 49 weeks post vaccination. Albeit a statistically significant difference in pox lesion scoring was measured, the clinical relevance of this difference is questioned. Another study was performed in SPF chicks, which supports a DOI of 34 weeks for reduction of clinical signs of FP.

The duration of immunity against ILTV was investigated in six studies in SPF birds vaccinated at 8 weeks of age with a vaccine with minimum titre rFP-LT. Challenges were performed at 12, 23, 41, 44, 52 and 57 weeks post vaccination. At 57 weeks p.v. the vaccine was found to be efficacious, with reduction of clinical signs and reduction of tracheal lesions. The results of the studies with earlier challenges confirm the continued protection against ILTV up to 57 weeks.

Duration of immunity against AEV was investigated in two studies in commercial layers, vaccinated at 8 weeks of age with Vectormune FP ILT + AE diluted to contain a minimum titre of AE component. In the two studies, animals were challenged at 43 and 57 weeks post vaccination. In vaccinated groups, a drop in egg production as observed in control groups was prevented, confirming continued immunity up to 57 weeks.

Based on literature data provided, it can be concluded that MDA is highly unlikely to play a role for FPV or ILTV in birds vaccinated from 8 weeks of age. For AEV, the laboratory (DOI) study supports efficacy in commercial (MDA+) layer pullets, vaccinated at the minimum age of 8 weeks.

No compatibility is claimed with any other medicinal product; an appropriate warning sentence is included in section 4.8 of the SPC.

The results obtained in three positive-controlled, combined safety and efficacy field trials generally support the efficacy claims for FP and ILTV; since no field challenge occurred, no data on efficacy against AEV were obtained.

Part 5 – Benefit-risk assessment

Introduction

Vectormune FP ILT + AE is a combination of a live recombinant FPV strain expressing the membrane fusion protein and the encapsidation protein of ILTV (rFP-LT) and an AEV, Calnek 1143 strain.

The vaccine is intended for active immunisation of layer chickens for protection against FP, ILT and AE.

The dossier was submitted in line with requirements of Article 12(3) of Directive 2001/82/EC.

Benefit assessment

Direct therapeutic benefit

The benefit of Vectormune FP ILT + AE is intended to be the active immunisation of layer pullets from 8 to 13 weeks of age;

- to reduce skin lesions caused by FPV,
- to reduce clinical signs and tracheal lesions due to ILTV,
- to prevent a drop in egg production caused by AEV,

which was shown in a number of appropriately designed and well executed laboratory and field studies.

OOI against FP and ILT infection at 3 weeks after vaccination was established. The OOI against AEV can be set at 20 weeks after vaccination. A DOI of 57 weeks p.v. was established for ILTV and AEV. A DOI of 34 weeks is supported for FPV.

Considering the minimum age for vaccination, efficacy for Vectormune FP ILT + AE is unlikely to be affected by MDA. For the AE component, efficacy was shown in the presence of residual MDA.

Additional benefits

Vectormune FP ILT + AE combines protection against three important poultry diseases. This limits the number of times the animals are required to be handled.

Vectormune FP ILT + AE reduces the need for live attenuated ILTV vaccination, and thus may help reduce the occurrence of new virulent strains due to recombination in the field.

Vectormune FP ILT + AE was shown to be apathogenic to other avian species, limiting the risk to the environment.

Risk assessment

The main potential risks are identified as follows:

Quality

The formulation and manufacture of Vectormune FP ILT + AE is well described, and specifications set will ensure that product of consistent quality will be produced, provided that conditions are fulfilled.

Safety

Risks for the target species:

The product is generally well tolerated in the target animal. No adverse reactions were observed after an overdose of Vectormune FP ILT + AE by the wing web route. The rFP-LT vaccine strain was obtained by insertion of genes into a vaccine strain, which is known to be safe for chickens. The biological properties (safety, dissemination, spread) of the original strain were not changed by the genetic modification. The AE vaccine strain is a well known vaccine strain. For either vaccine strain, reversion to virulence could not be demonstrated. The chance of recombination with other strains or other viruses occurring is considered to be effectively zero.

Risks for the user:

The user safety for this product is acceptable when used as recommended.

Risks for the environment:

The rFP-LT vaccine virus did not spread to susceptible in-contact chickens; the AE vaccine strain does spread and shed virus and can remain infectious in the environment for prolonged periods. Safety and spreading of the rFP-LT strain was investigated in turkeys, ducks, quail, guinea fowl and pigeons: There were no safety issues, a low frequency (5%) of spreading was observed in all species tested. Fowlpox virus can infect avian species only, the vaccine strain was shown to be unable to infect mice or pigs.

For the consumer:

A residue study is not required. The withdrawal period is set at zero days.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks of this product relevant to the target animal, user and environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The benefit-risk balance of the application is considered to be positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Vectormune FP ILT+AE is approvable, since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above-mentioned medicinal product.