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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Vectormune FP ILT (EMA/V/C/005482/0000)

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

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



Introduction.....	4
Scientific advice.....	4
MUMS/limited market status	4
Part 1 - Administrative particulars	4
Detailed description of the pharmacovigilance system	4
Manufacturing authorisations and inspection status.....	5
Overall conclusions on administrative particulars	5
Part 2 – Quality	5
Chemical, pharmaceutical and biological/microbiological information (quality)	5
Qualitative and quantitative particulars of the constituents	5
Qualitative and quantitative particulars	5
Container and closure	5
Product development	6
Description of the manufacturing method	6
Production and control of starting materials	6
Starting materials listed in pharmacopoeias	7
Specific materials not listed in a pharmacopoeia	7
Starting materials of biological origin	7
Starting materials of non-biological origin	7
In-house preparation of media and solutions consisting of several components	7
Control tests during the manufacturing process	7
Control tests on the finished product.....	7
Batch-to-batch consistency	8
Stability.....	8
Overall conclusions on quality	8
Part 3 – Safety	9
Introduction and general requirements.....	9
Safety documentation	9
Laboratory tests	10
Safety of the administration of one dose.....	10
Safety of one administration of an overdose.....	10
Safety of the repeated administration of one dose	11
Examination of reproductive performance	11
Examination of immunological functions	11
Special requirements for live vaccines	11
Spread of the vaccine strain.....	11
Dissemination in the vaccinated animal	12
Reversion to virulence of attenuated vaccines	12
Biological properties of the vaccine strain	12
Recombination or genomic reassortment of the strains.....	12
User safety	13
Study of residues.....	13
Excipients	13

MRLs.....	13
Withdrawal period.....	13
Interactions	13
Field studies.....	13
Environmental risk assessment	16
Considerations for the environmental risk assessment.....	17
Environmental risk assessment for products containing or consisting of genetically modified organisms.....	17
Overall conclusions on the safety documentation	17
Part 4 – Efficacy	18
Introduction and general requirements.....	18
Challenge model:	19
Efficacy parameters and tests:	19
Efficacy documentation	19
Laboratory trials.....	20
Dose determination.....	20
Onset of immunity	20
Duration of immunity	21
Maternally derived antibodies (MDA)	22
Interactions	23
Field trials.....	23
Overall conclusion on efficacy.....	25
Part 5 – Benefit-risk assessment	26
Introduction.....	26
Benefit assessment.....	26
Direct therapeutic benefit	26
Additional benefits	27
Risk assessment.....	27
Risk management or mitigation measures	27
Evaluation of the benefit-risk balance.....	28
Conclusion	28

Introduction

The applicant Ceva-Phylaxia Co. Ltd submitted on 27 January 2020 an application for a marketing authorisation to the European Medicines Agency (the Agency) for Vectormune FP ILT, 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 8 November 2019 as Vectormune FP ILT has been developed by recombinant DNA technology.

Vectormune FP ILT is a live, genetically modified organism (GMO), virus vaccine consisting of a recombinant fowlpox virus expressing the membrane fusion protein and the encapsidation protein of avian infectious laryngotracheitis virus.

The applicant applied for the following indications: For active immunisation of chickens from 8 weeks of age in order to reduce the skin lesions due to fowlpox and to reduce the clinical signs and tracheal lesions due to avian infectious laryngotracheitis. The product is intended for chickens for administration by wing-web-stab use with the help of a pronged applicator.

Vectormune FP ILT 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 was Jacqueline Poot and the co-rapporteur was Cristina Muñoz Madero.

The dossier was submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC – full application.

On 7 October 2020, the CVMP adopted an opinion and CVMP assessment report.

On [9 December 2020](#), the European Commission adopted a Commission Decision granting the marketing authorisation for Vectormune FP ILT.

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.

Solvent manufacturing, packaging and QC, as well as secondary packaging of the lyophilisate and solvent is performed both at the site in Budapest and 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 substance 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 ingredient in the vaccine is a live recombinant FPV vaccine strain, expressing the gB and UL-32 genes of ILTV.

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

closures with or without a plastic tear-off cap.

The containers and closures are in compliance with the pharmacopoeial requirements and their sterilisation is adequate. The applicant has stated that 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.

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.

Vectormune FP ILT + AE, a larger combination vaccine, was used for all clinical studies. The formulation and manufacturing method of Vectormune FP ILT + AE is identical to that of Vectormune FP ILT but for the addition of the AE component. The composition of the batches used in clinical studies is therefore considered the same as that intended for marketing.

Description of the manufacturing method

The manufacturing process consists of two main steps: the production of the rFP-LT virus 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.

The finished product is blended to achieve a target titre of virus. The final composition is composed of the active substance 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 manufacturing process for the freeze-dried vaccine has been validated by four consecutive batches. It has 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 controls are adequate for this type of manufacturing process.

Production and control of starting materials

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 have been assessed. The conclusion that the risk for transmission of extraneous agents with this product is negligible is supported.

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 MSV was tested in accordance with relevant Ph. Eur. monographs.

Starting materials of non-biological origin

A CoA has been provided for Patent blue V (E131), which conforms to in-house specifications.

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 the following control tests: titration of rFP-LT virus, sterility 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 test of rFP-LT virus is performed by immunostaining of infected cells. Absence of mycoplasmas 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 limits proposed for residual humidity of the lyophilisate were adequately justified.

Batch-to-batch consistency

Manufacturing details and results of in-process and finished product testing of four consecutive batches of freeze-dried vaccine are summarised in tabular format. The batches conformed to the requirements for all in-process and finished product tests.

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

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

Stability

Data on the stability of the bulk active ingredient were provided. The bulk antigens can be stored for 15 months at -20 °C.

Real-time stability data of four batches of Vectormune FP ILT + AE finished product stored for 24 months at 2-8 °C were provided. The manufacturing method and composition of these batches is identical to those proposed for marketing of Vectormune FP ILT, except for the AE component. Batches were packed in the primary packaging proposed for marketing. Results show no loss in titre for rFP-LT over the 24-month storage period. The data are considered suitable and support a shelf life of 21 months for the lyophilisate.

Furthermore, an in-use shelf life of 2 hours after reconstitution is sufficiently demonstrated based on data generated with the larger combination vaccine.

Three batches of solvent were tested for real-time stability over 36 months. All parameters remained within specifications. The data support the proposed shelf life of 36 months.

Overall conclusions on quality

Vectormune FP ILT is a live vaccine for active immunisation of chickens against fowlpox (FP) and infectious laryngotracheitis (ILT). The vaccine is available in glass vials containing 1000 or 2000 doses and is diluted before use in solvent supplied in glass vials. Satisfactory information on packaging materials was provided.

The information provided on the qualitative and quantitative composition is generally acceptable. The manufacturing method can be considered standard for this type of vaccine.

Starting materials are generally of satisfactory quality.

The procedures implemented to ensure the absence of extraneous agents in starting materials of animal origin are generally 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 (IPC) and quality control on the finished product (FPC) 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 performed on the larger combination product show no loss in infectivity titre for the rFP-ILT component during a 24-month storage period at 2-8 °C. Data are considered to support the proposed 21-month shelf life. Stability data of reconstituted Vectormune FP ILT + AE show that the vaccine remains stable at room temperature for 2 hours, therefore the proposed 2 hours in-use shelf life

can be accepted for this vaccine also. The proposed 36-month shelf life of the solvent is supported by the data presented.

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 is a live vaccine intended for active immunisation of chickens to reduce skin lesions due to fowlpox and to reduce clinical signs and tracheal lesions due to avian infectious laryngotracheitis. The active substance, rFP-LT, is a genetically modified organism.

Vectormune FP ILT is a fall-out of Vectormune FP ILT + AE and therefore part 3 of this dossier is identical to the one submitted for Vectormune FP ILT + AE, except that the information concerning the AE component was removed. In accordance with CVMP Guideline EMA/CVMP/IWP/594618/2010 ('Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products [IVMPs]'), safety studies conducted with the largest combination of a vaccine are considered as the worst case for smaller combinations. As a consequence, studies for safety of single dose, repeated dose and overdose as well as field safety trials were not repeated using Vectormune FP ILT. This is considered acceptable.

Safety documentation

Thirteen safety studies were conducted, including 10 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 of Vectormune FP ILT + AE containing 5.4 log₁₀ TCID₅₀ FP-LT and 5.28 log₁₀ EID₅₀ AE per dose. Production batches of Vectormune FP ILT + AE 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.

<i>Study title</i>
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
Dissemination in animal of wing web-administered rFP-LT MSV in SPF chickens
Reversion to virulence and overdose (10x) safety of wing web-administered rFP-LT 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 this marketing authorisation dossier, except for the AE component.

For evaluation of the dissemination, spread and increase in virulence studies, an FPV PCR test was used. Validation of this test has been provided and the suitability was adequately justified.

Safety of the administration of one dose

The safety of the administration of a single 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 one supportive overdose laboratory study were provided.

The pivotal study was compliant with GLP standards. An overdose of the Vectormune FP ILT + AE vaccine containing 5.4 log₁₀ TCID₅₀ FP-LT per dose, which equals to 7.9 times the recommended dose for rFP-LT, 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 at 1 and 4 hours after vaccination and clinical signs were monitored daily from Day 0 to Day 21. Body weight was recorded on Days 0, 7, 14 and 21. The injection site was inspected on Days 7, 14 and 21. Post-mortem macroscopic and microscopic examinations were performed on Days 7, 14 and 21.

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 at D14 and D21 or in diluent controls. 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.

In a supportive study, the safety of rFP-LT MSV at 5.5 log₁₀ TCID₅₀ per dose, which equals to 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.

On the basis of the results, no safety concerns arose following the administration of an overdose of Vectormune FP ILT + AE containing rFP-LT at 7.9 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 viral component 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 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. The vaccine virus was shown to be cleared from vaccinates within 28 days after vaccination and thus before the point of lay. The indicated treatment window is after the maturation of the birds' reproductive system and before reproductive maturity. 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 studies were conducted to specifically investigate the effects of the product on immunological functions. The parent virus is not known to be immunosuppressive, from which it is concluded that the attenuated vaccinal strain will have no impact on immunological functions. Some FPV field strains harbour a retrovirus sequence (reticuloendothelial virus [REV]) which is immunosuppressive; these strains appear more pathogenic to chickens. The absence of a full REV genome sequence was verified for various FP vaccinal strains, including the TCP-Blen strain from which this vaccine derives.

Special requirements for live vaccines

Spread of the vaccine strain

The spread of the vaccine strain from vaccinated to unvaccinated animals was investigated in a study in which 5-week old SPF chickens were vaccinated with a single maximum dose of the vaccine virus (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 rFP-LT vaccine strain was not found in any of the sentinel tissues sampled or in any of the cloacal or oral swabs of the vaccinates or contact animals. It is concluded that the rFP-LT vaccine virus is unlikely to spread to in-contact unvaccinated animals. No evidence of shedding from vaccinated animals was obtained.

Six studies were carried out to investigate spreading of rFP-LT 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 for the recombinant rFP-LT strain and/or the parent FP strain in all species tested. 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 target animals was investigated. 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.

In conclusion, the virus strain disseminates following vaccination by the recommended route of a single maximum dose in 5-week old SPF chickens. The rFP-LT virus can be present in vaccinates for up to 28 days post vaccination.

Although Vectormune FP ILT 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 strain may persist at the injection site or in the organs and tissues for up to 4 weeks.

Reversion to virulence of attenuated vaccines

The reversion to virulence of the vaccine strain was investigated in accordance with the requirements of Ph. Eur. 5.2.6 and Ph. Eur. 0442 monographs, respectively.

Sequential passage of the 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 animals 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* of the rFP-LT vaccine strain.

Biological properties of the vaccine strain

The vaccine strain is derived from a well-known and globally used vaccine strain (parent FP strain). The properties of the rFP-LT strain are further detailed in part 3.E.

Recombination or genomic reassortment of the strains

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 guideline 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 accidental self-injection and dermal and/or oral exposure are the most likely to occur. The vaccine virus is not pathogenic for humans and therefore does 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 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 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 and partly blinded field studies were conducted to

evaluate safety and efficacy of Vectormune FP ILT + AE. 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 the 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: Vectormune FP ILT + AE Group 2: CVP 1 and CVP 2: Cevac FP L and Avipro AE
Control product/ Placebo	
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 body weight was consistently slightly higher in Group 2 compared to Group 1; however, the difference was 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: 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 (Days 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
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Objectives	To evaluate safety and efficacy of Vectormune FP ILT + AE under field conditions
Test product	Group 1: IVP: 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. A 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 weeks 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 body 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 relevant CVMP note for guidance (EMA/CVMP/074/95).

Considerations for the environmental risk assessment

FP viruses have the capacity to transmit to non-target (avian) species. 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. The virus has no capacity to transmit to non-avian species.

The vaccine virus cannot multiply in the environment. The vaccine is applied by injection, which precludes its dispersion in the environment. The rFP-LT strain was shown not to be shed, and survival in the environment was shown to be limited.

All 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 is expected to pose a negligible risk to the environment when used as recommended.

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

Vectormune FP ILT 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 cassette-containing ILT gB and UL-32 genes as well as the *E. coli* LacZ gene, under the control of synthetic consensus poxvirus promoters. 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

Vectormune FP ILT + AE routine production batches were used in the safety studies. This is acceptable, since Vectormune FP ILT is considered a fall-out of this larger combination vaccine. The applicant has provided one pivotal laboratory study to investigate the safety of an overdose to target animal species of the minimum recommended age via the recommended wing-web route. Repeated administration was not investigated. This is accepted since the vaccine is to be applied by a single lifetime injection. No clinical signs or mortality were observed in any of the birds, except for local reactions indicative of vaccine take (small scab). An overdose of the rFP-LT MSV was shown to be safe.

Reproductive performance was not studied and therefore 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 and dissemination was very limited.

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

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

The user safety has been adequately addressed and an appropriate 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 is not expected to pose a risk to the environment when used in accordance with the SPC.

Since the rFP-LT strain 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 foreign proteins did not change the virulence in the target species or other avian species or mammals. Any risk emerging from the use of the rFP-LT vaccine virus is considered to be negligible for humans and the environment.

Three studies were performed investigating the safety of the vaccine when applied under field conditions. Based on the 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 is intended for active immunisation of chickens to reduce skin lesions due to FP and to reduce clinical signs and tracheal lesions due to ILT.

The vaccine is intended to be administered to layer chickens from 8 weeks of age onwards and prior to the onset of lay. Immunity is intended to be established 3 weeks after a single injection for FP and ILT.

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

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

Vectormune FP ILT is a fall-out of Vectormune FP ILT + AE; this dossier part 4 is identical to the one submitted for Vectormune FP ILT + AE, except that the information concerning the AE component was removed. In accordance with CVMP Guideline EMA/CVMP/IWP/594618/2010 (Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)), efficacy studies conducted with the largest combination of a vaccine are considered acceptable for smaller combinations, provided the components are identical. As a consequence, studies for onset and

duration of immunity, as well as field efficacy trials were not repeated using Vectormune FP ILT; this is considered acceptable.

Challenge model:

For FP, the FP-SBS challenge strain was used.

For ILT the challenge strain was sourced from USA. This US strain is relevant to European field strains since ILTV is considered to be antigenically homogenous.

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 and general and respiratory clinical signs, mortality and tracheal lesions for ILT. The parameters chosen are considered appropriate for evaluating the claimed efficacy of the product.

Efficacy documentation

Nineteen studies were conducted to investigate the efficacy of the product; this included 16 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 of Vectormune FP ILT + AE.

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
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
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 TCID₅₀ for the rFP-LT vaccine strain was established based on the findings of a dose determination study. Vaccine applied at doses of 2.66 log₁₀ TCID₅₀ and 3.0 log₁₀ TCID₅₀ 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 TCID₅₀ group, however, all animals were significantly protected from clinical signs of fowlpox.

Onset of immunity

Three studies were performed, two 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 TCID₅₀ 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-SBS strain, animals were observed daily for clinical signs (of FP) 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 TCID₅₀ 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.

A study investigated onset of immunity against ILTV 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 TCID₅₀ 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.

Duration of immunity

Eight 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 and six for ILTV.

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 TCID₅₀ of the rFP-LT component in 0.01 ml; vaccine take was checked and found to be 100% in both studies.

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

65% of vaccinates showed notable pox lesions (\geq 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 duration of immunity study against ILTV at 65 weeks of age 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 EID₅₀ of ILTV. Respiratory and general clinical observations were performed daily for one week; tracheal lesions were scored at Day 8.

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 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 EID₅₀ (12, 23 weeks), 2.5 log₁₀ EID₅₀ (41, 52 weeks) and 2.2 log₁₀ EID₅₀ (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.

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 there was 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.

Taken together, it can be concluded that MDA are highly unlikely to play a role for FPV or ILTV in birds vaccinated at 8 weeks of age.

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 or ILT 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.

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 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.

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	Vectormune FP ILT + AE
Control product/ Placebo	CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Efficacy parameter	<p>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 .</p> <p>Complementary FPV challenge: In Group 3 no animals showed notable pox lesions; in Group 1, 50% of birds showed notable pox</p>

	<p>lesions, with a total average score of 45.4. In Group 2, 85% of birds showed notable pox lesions with a total avg. score of 68.6. The average score in Group 1 was significantly lower than in Group 2.</p> <p>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.</p>
Discussion	
Discussion/conclusions further to assessment	The design and execution of the study was adequate. No outbreaks of FP or ILT occurred. The results of the complementary challenges with FPV and ILTV at 23 and 28 weeks post vaccination, respectively, support the results of the laboratory challenge studies. Prevention of mortality due to ILTV was not achieved in this study.

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
Interventions: Vaccine	Vectormune FP ILT + AE
Control product/ Placebo	CVP 1 and CVP 2: Cevac FP L and Avipro AE
Results	
Efficacy parameter	No outbreaks of FP or ILT 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	The design and execution of the study was adequate. The age of

further to assessment	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. No data on protection against FP and ILT were obtained.
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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: Vectormune FP ILT + AE
Control product/ Placebo	Group 2: CVP 1, CVP 2 and CVP3: Hiprapox, Poulvac ILT and Bio EA
Results	
Efficacy parameters	No outbreak of FP or ILT occurred. Vaccine take was observed in 92/100 birds in Group 1 and 99/99 birds of Group 2. From 4 weeks post vaccination, 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. 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.

Three 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 rFP-LT.

Onset of immunity against FPV was shown at three weeks post vaccination by reduction of clinical signs 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 intra-tracheal route.

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

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 for up to 57 weeks.

Based on literature data provided, it can be concluded that MDA are highly unlikely to play a role for FPV or ILTV in birds vaccinated from 8 weeks of age.

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 FPV and ILTV.

Part 5 – Benefit-risk assessment

Introduction

Vectormune FP ILT is a live vaccine containing a recombinant FPV strain expressing the membrane fusion protein and the encapsidation protein of ILTV (rFP-LT).

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

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 LT is intended to be the active immunisation of layer pullets from 8 weeks of age:

- to reduce skin lesions caused by FP,
- to reduce clinical signs and tracheal lesions due to ILT,

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

Onset of immunity against FP and ILT infection at 3 weeks after vaccination was established.

A duration of immunity of 34 weeks post vaccination was established for FPV and 57 weeks post vaccination for ILTV.

Considering the minimum age for vaccination, efficacy for Vectormune FP LT is unlikely to be affected by maternally derived antibodies.

Additional benefits

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

Vectormune FP ILT 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 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 is well described and specifications set will ensure that product of consistent quality will be produced provided that specified parameters are met.

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 LT 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. 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. 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.

Risks 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 and other product information to inform on the potential risks of this product relevant to the target animal, user, the environment and consumer, and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The applicant applied for the following indication: "for active immunisation of chickens from 8 weeks of age in order to reduce the skin lesions due to fowlpox and to reduce the clinical signs and tracheal lesions due to avian infectious laryngotracheitis".

The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Based on the data presented, the overall benefit-risk balance is considered positive.

Conclusion

Based on the CVMP review of the original and complementary data on quality, safety and efficacy, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Vectormune FP ILT 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.