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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Innovax-ILT (EMEA/V/C/003869/0000)

Common name: Avian infectious laryngotracheitis and Marek's disease vaccine (live)

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

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Introduction

On 20 February 2014 the applicant Intervet International B.V. submitted an application for a marketing authorisation to the European Medicines Agency (the Agency) for Innovax-ILT under Article 3(1) of Regulation (EC) No. 726/2004 (biotechnological veterinary medicinal product).

The eligibility to the centralized procedure was agreed upon by the CVMP on 10 October 2013 as the product is manufactured by means of a biotechnological process (Article 3(1) of Regulation (EC) No. 726/2004). The rapporteur appointed was E. Werner and the co-rapporteur was J. Bureš.

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

Innovax-ILT is a live virus vaccine intended for the active immunization of chickens of one day of age to reduce mortality, clinical signs and lesions of infectious laryngotracheitis (ILT) and Marek's disease (MD). It contains as active substance a live recombinant serotype 3 herpesvirus of turkey (HVT) with inserted the D and the I glycoprotein genes from an infectious laryngotracheitis virus (ILTV) with a range of titre of $10^{3.1}$ – $10^{4.1}$ PFU per dose of 0.2 ml.

The product is a frozen cell suspension stored in liquid nitrogen. It is presented in 2 ml sealed glass ampoules containing 2,000 or 4,000 doses. The solvent is presented in plastic bags of 400 ml and 800 ml respectively. Dilution with the solvent for suspension for injection is required before injection into chicken.

On 7 May 2015, the CVMP adopted an opinion and CVMP assessment report.

On 3 July 2015, the European Commission adopted a Commission Decision granting the marketing authorisation for Innovax-ILT.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

A version of the detailed description of the pharmacovigilance system (DDPS) (version 1.0, 1.4.2014), which fulfils the requirements of Directive 2001/82/EC, was provided.

A statement signed by the applicant and the qualified person responsible for pharmacovigilance (QPPV), indicating that the applicant has the services of a QPPV available and the necessary means for the collection and notification of any adverse event occurring either in the EEA or in a third country (non EEA) as well as a summary of the QPPV job description. There are no outstanding issues.

Manufacturing authorisations and inspection status

A number of sites are involved in the manufacture and quality control (QC) of Innovax-ILT and the solvent.

Production of the cell suspension takes place at Intervet Inc., Millsboro (USA). Batch release of the final product, including the solvent is performed at Intervet International B.V. at Boxmeer (the Netherlands).

Manufacturing authorisations and valid GMP inspection certificates for all sites were provided.

Overall conclusions on administrative particulars

The GMP certification of the manufacturing sites and the detailed description of the pharmacovigilance system were provided and were considered in line with legal requirements.

Part 2 – Quality documentation

Innovax-ILT is a veterinary vaccine intended for the active immunisation of chickens against MD and ILT. Innovax-ILT is a live, frozen, cell-associated vaccine containing the recombinant serotype 3 herpes virus of turkeys (HVT) strain FC-126 related to the Marek's disease virus of chickens (MDV). It was genetically modified by inserting the D and I glycoprotein genes from ILTV. No adjuvants or preservatives are added. The vaccine is mixed with the solvent prior to subcutaneous (SC) injection into chickens.

Composition

Innovax-ILT is a live, frozen cell-associated viral suspension containing the active ingredient and a solvent for reconstitution. The pharmaceutical form is a suspension for injection. The active ingredient is the live herpesvirus of turkey strain HVT/ILT-138 (HVT-based recombinant encoding glycoproteins gD and gI of ILTV) with a range of titre of $10^{3.1}$ – $10^{4.1}$ PFU (plaque forming units) per dose of 0.2 ml of reconstituted vaccine. The vaccine also contains three excipients: a cryoprotectant, such as dimethyl sulfoxide and two stabilisers, namely bovine serum and basal medium.

The solvent for reconstitution contains sucrose and pancreatic digest of casein as stabilizer, potassium dihydrogen phosphate as buffer, phenolsulfonphthalein (phenol red) as indicator and water for injections.

The qualitative and quantitative particulars of the vaccine and solvent are described adequately and in compliance with European Pharmacopoeia (Ph. Eur.) or other respective regulations.

Container

Innovax-ILT is presented in type I glass ampoules with a volume of 2 ml which are flame sealed after filling then frozen and stored in liquid nitrogen. Presentations for sale will contain 2,000 or 4,000 doses.

The solvent is presented in polyethylene (PE) or multilayer plastic (MLP) bags. Matching the number of doses of the vaccine, two presentations of a solvent will be authorised with the vaccine, comprising 400 ml and 800 ml bags.

The container and closures comply with Ph. Eur.

Development pharmaceutics

Vaccinations against MD and ILT are common in poultry flocks. All chickens are vaccinated against MD on the first day of life with live attenuated MDV vaccine strains and/or apathogenic herpesvirus of turkeys (HVT) strains. Vaccinations against ILT are also performed using live attenuated vaccines; however, the risk of serious adverse events is much higher. Therefore, chickens are vaccinated not before 4 weeks of age. Innovax-ILT was developed to improve the safety profile and for vaccination of chickens from one day of age. Two (2) glycoprotein genes of ILTV, namely I and D (gI and gD) were inserted into the genome of HVT strain FC-126. HVT is a good vector candidate, as it hardly spreads, is fully apathogenic and it is not infectious for non-avian species. The objective of this development was to enable ILT vaccination for chickens without the use of live ILTV vaccines.

The final formulation of a liquid vaccine frozen in liquid nitrogen and diluted in a solvent before injection into chickens was chosen because of the special properties of avian herpesviruses. The virus is cell-associated; therefore, it is propagated on chicken embryo fibroblasts (CEF), cells are harvested, stabilised, frozen and stored in liquid nitrogen. The vaccine is then injected SC after dilution in the corresponding stabilising solvent.

Cell-associated viruses need a certain environment to remain stable. The solvent is a stabilizing solution containing sucrose, pancreatic digests of casein and potassium dihydrogen phosphate. Phenolsulfonphthalein (phenol red) is added as an indicator.

Method of manufacture

The production process of Innovax-ILT is considered as standard manufacture for MD vaccines. Primary CEF cell cultures are prepared and seeded into culture flasks to generate monolayers. The monolayers are infected with virus. Subsequently, cells are harvested using trypsin, centrifuged and counted. Cell concentration is adjusted and stabiliser is added. The vaccine suspension is constantly agitated and filled in sterile 2 ml glass ampoules using an automated filling and sealing machine. After labelling the product is frozen in a programmable freezer and stored in liquid nitrogen. Production of the vaccine is satisfyingly described. The solvent used is routinely used along with other MD vaccines from Intervet International B.V. The information on the manufacture and control of the solvent was recently updated and approved. All information on the solvent is duly provided.

Control of starting materials

Active substance

The active substance is the live herpesvirus of turkey strain HVT/ILT-138, a HVT-based recombinant strain encoding gD and gI of ILTV, with a range of titre of $10^{3.1}$– $10^{4.1}$ PFU (plaque forming units) per dose.

Specifications of the active ingredient are defined and analytical methods are provided.

Excipients

Specifications of excipients and other starting materials (e.g. materials of biological and non-biological origin, media) are defined and analytical methods are provided. These are bovine serum, dimethyl sulfoxide and basal medium. Where applicable, the starting materials are in compliance with Ph. Eur.

or other respective regulations.

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

The documentation provided for all the materials of animal origin demonstrated their compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) and Commission Directive 1999/104/EEC.

Furthermore, the vaccine is intended for use in chickens which are not a transmissible spongiform encephalopathy (TSE) susceptible species.

It is concluded that, the risk of transmitting TSE infectivity through the use of this vaccine is negligible.

Control tests during production

During manufacture the following in-process control tests are carried out to ensure the quality parameters: check on cytopathic effect (CPE), cell count: determination of viable cells, check on filling volume.

Test descriptions and limits of acceptance are presented. The in-process controls are appropriate, adequately performed and described. Results from the testing of 3 consecutive batches are provided and well within the specifications.

No in-process control tests during production of the solvent are performed and this is acceptable.

Control tests on the finished product

The control on the finished product is performed on the filled product and is carried out to ensure the quality parameters. The following tests are performed: identification of active substance, virus titration (batch titre), sterility and purity tests, mycoplasma testing, and extraneous agents in embryonated eggs and on cell cultures.

Test descriptions and limits of acceptance are presented and satisfactory.

The validation of the immunofluorescence test method used within the framework of the virus titration was supplemented and was regarded as sufficient.

The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product.

The following finished product quality control tests are carried out on the solvent: pH value, sucrose content, clarity, appearance, content on average.

The results of the analysis of 3 consecutive production runs of vaccine and for 3 consecutive production batches of solvent were presented which comply with the required specifications.

Stability

Stability data were provided for 3 batches of Innovax-ILT produced for the US market containing 0.5 mg/ml gentamicin. These data support a shelf life of 36 months. Three (3) batches without gentamicin are currently being tested for stability. The latest time point tested was 29 months.

Additional data on the EU-batches are expected to be provided as soon as they will be available.

The proposed in-use shelf life is 2 hours which is supported by data for in-use stability of 3 hours showing no significant loss in titre during this time.

The proposed shelf life of the solvent is 36 months in PE bags and 24 months for MPL bags.

Overall conclusions on quality

Information regarding the qualitative and quantitative composition, the starting materials, production method, quality controls and stability are provided and are acceptable. Test results of consecutive batches of Innovax-ILT were presented in order to demonstrate batch-to-batch consistency.

The production process is described in detail.

All starting materials are defined and comply with the provisions of Ph. Eur., where applicable.

The main risks concerning TSE are considered negligible.

The respective certificates of suitability are provided. The in-process and finished product controls performed ensure a consistent production of Innovax-ILT.

In conclusion, the production and quality control of Innovax-ILT are adequately described and comply with the respective legal requirements including the TSE risk assessment.

Part 3 – Safety documentation

Introduction

In the safety studies provided, Innovax-ILT was administered to one-day-old chicks according to the recommended vaccination scheme by the SC route.

A study was provided in which a 10-fold overdose ($10^{5.1}$ PFU/dose) of Innovax-ILT, and an overdose of Innovax-ILT mixed with an overdose of the authorised product Nobilis Rismavac (containing the Rispens CVI-988 strain of MDV) were administered. In the same study, the potential reversion to virulence of the vaccine strain was investigated, by inoculation of the 5^{th} back passage of the MSV+4 passage of the vaccine strain.

Studies were provided investigating the spread of an overdose of Innovax-ILT from vaccinated chickens to contact chickens and contact turkeys as well as replication and spread in several non-target avian species (turkeys, ducks, pheasants, quails) and to one mammalian species (mice). The dissemination of the modified HVT/ILT-138 strain in chickens in comparison to its parental strain was also investigated. Another two studies examined the possibly altered immunological functions and the reversion to virulence respectively. Furthermore, the potential interaction between Innovax-ILT and the product Nobilis ND Clone 30 mixed with the product Nobilis ND C2 (both vaccines against Newcastle disease (ND)) applied on the same day at different sites was investigated. In addition, 2 field studies were conducted examining the mixed application of Innovax-ILT and Nobilis Rismavac. The safety of a single dose, the repeated administration of a single dose and safety for the reproductive tract were not investigated, which is acceptable.

Laboratory tests

All laboratory tests were carried out in compliance with Ph. Eur. monographs 0062 on vaccines for veterinary use, Ph. Eur. chapter 5.2.6 on evaluation of safety of veterinary vaccines and immunosera, Ph. Eur. monograph 0589 on MDV (live), Ph. Eur. monograph 1068 on avian ILTV (live), Ph. Eur. monograph 0450 on Newcastle disease vaccine (live) and with the CVMP Guideline on the requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs) (EMA/CVMP/IWP/594618/2010).

Nine (9) Good Laboratory Practice (GLP) compliant studies were carried out with Innovax-ILT. Safety and relevant performance measures were investigated in two (2) field trials.

Safety of the administration of one dose

As a single dose safety testing is not required according to Ph. Eur. monograph 0589 and no separate single dose study has been conducted by the applicant. This approach is accepted as an overdose study is provided, which represents the worst case scenario.

Safety of one administration of an overdose

The safety of a 10-fold overdose ($10^{5.1}$ PFU/dose/0.2ml/animal) administered to one-day-old specific pathogen free (SPF) chick by the SC route was tested in one (1) study. Hundred seventy-six (176) chickens were used in this study and divided in 4 groups of 44 chickens each. In group 1, 44 chickens were vaccinated with 5th back passage of Innovax-ILT. In group 2, 44 chickens were vaccinated with 10-fold overdose of Innovax-ILT, (for comparison of the results of groups 1 and 2, please see section "reversion to virulence"). In group 3, 44 chickens were vaccinated with 10-fold overdose of Innovax-ILT mixed with 10-fold overdose of Nobilis Rismavac. In group 4, 44 chickens were used as controls and inoculated with very virulent MDV (RB1B) at the age of 7 days to demonstrate the susceptibility of the used SPF chickens.

This study meets the requirements of Ph. Eur. monograph 0589 concerning safety.

No signs of MD were observed during clinical and pathological examination except in the challenged positive control group 4. ILT-symptoms or lesions are not explicitly excluded. However, it is assumed that if clinical signs or lesions suspect of an ILT infection had occurred, those signs would have been recorded and described. Several minor clinical signs were seen in a large number of birds in groups 1 and 3, which are considered not attributable to the vaccine. It was reported that the feed regime was changed during the study which is proposed to explain the observation. Suitable information on the used challenge strain is provided.

Based on an assessment of the data there is no reason to believe that Innovax-ILT would not be safe after SC administration to one-day-old chicks. An expert opinion was provided in which the possible future implications regarding recombination by the mixed application with MD serotype 1 Rispens strain CVI988 were summarized and assessed as negligible.

Safety of the repeated administration of one dose

No study to assess the safety of the repeated administration of one dose was performed as Innovax-ILT is intended to be administered only once at one day of age. This is in accordance with Directive 2001/82/EC. Nevertheless, as the applicant accidentally inoculated some birds twice in one of the performed studies, the accidentally repeated inoculation seems to be a possible scenario.

The 2 double vaccinated birds (with a 10-fold overdose) developed no clinical signs or macroscopic lesions afterwards. In addition, most of the provided studies are performed with a 10-fold overdose of Innovax-ILT. Results show that a 10-fold overdose of Innovax-ILT is safe. The safety of a 10-fold overdose of Innovax-ILT mixed with a 10-fold overdose of Nobilis Rismavac was also examined. Moreover, the 10-fold overdose of both Innovax-ILT mixed with Nobilis Rismavac was also demonstrated to be safe.

An accidentally given second injection of a single dose seems to be a lesser burden for a chicken than the overdose vaccination which proved to be safe. In conclusion, the omission of this study is acceptable.

Examination of reproductive performance

The parental strain HVT FC-126 of the vaccines strain HVT/ILT-138 is not known to affect the reproductive performance of chickens and is generally considered apathogenic, like in its host species turkey. This is demonstrated by several studies. By contrast, infection with ILTV may cause performance losses and decreased egg production in affected flocks.

In the provided field trial in the US layer chickens were vaccinated with Innovax-ILT mixed with Rismavac and a control group was vaccinated with RIS-MA (both authorised in USA, the former equal to Nobilis Rismavac (containing the MDV Rispens CVI-988 strain), the second equal to Nobilis Rismavac+CA126 (containing the MDV Rispens CVI-988 strain and the HVT FC-126 strain). Representative commercial batches were used. Weekly egg production was followed up to 60 weeks and no differences could be noticed in the group vaccinated with Innovax-ILT compared to the control group. No differences were found in other parameters observed. Innovax-ILT does not affect the egg production, if the vaccine is administered as recommended and as demonstrated in the field study.

In the field trial in the Netherlands one-day-old chicks of the layer type were vaccinated with Innovax-ILT mixed with Nobilis Rismavac and the control group was vaccinated with Nobilis Rismavac+CA126, but only monitored for 12 weeks afterwards. Therefore, it was not possible to observe a potential influence on the reproductive performance but it could be noted that no differences (morbidity, mortality, weight gain, local reactions) between the test group and the control group could be noted.

Pharmacovigilance data from the use of Innovax-ILT in the field outside the European Union (EU) do not indicate any issue with regard to lay or reproductive performance, and this is considered acceptable. Moreover it is acceptable that the possible effects of the two inserted genes from ILTV encoding for the gD and the gI were not discussed as no negative consequences attributable to the use of Innovax-ILT are noticeable in the field trials. The lack of information on the use of Innovax-ILT in breeding birds is reflected in the summary of product characteristics (SPC).

Examination of immunological functions

The parent strain HVT FC-126 is known to have no immunosuppressive properties. Nevertheless, the insertion of gD and gI genes may affect the properties of the newly constructed strain. Therefore, the potential immunosuppressive properties of vaccine strain HVT/ILT-138 were investigated by a vaccination-challenge experiment through vaccination with Nobilis ND Clone 30 2 weeks after vaccination with Innovax-ILT at one-day of age.

One group of 22 chickens was vaccinated by the SC route with a 10-fold overdose of Innovax-ILT and a fortnight later with Nobilis ND Clone 30 per eye-drop. For comparison the second group of 22 chickens was only vaccinated with Nobilis ND Clone 30 at 15 days of age. An unvaccinated control

group (22 chickens) was included. Three (3) weeks afterwards all groups were challenged with a velogenic Newcastle disease virus (NDV) strain Herts 33/56 (required by Ph. Eur. monograph 0450) and were clinically observed.

Both vaccination groups were fully protected against challenge. No lesions related to the challenge virus could be found after sacrifice. All unvaccinated control chickens developed severe clinical signs of ND and were euthanized.

No pathological examinations to assess the development of relevant organs like bursa and thymus were performed but relevant organs were examined in another study.

Innovax-ILT seems to have no negative effect on the immunological functions if administered at a 10-fold overdose ($10^{5.1}$ PFU/dose) when given to one-day-old chicks.

Special requirements for live vaccines

An additional study was performed to determine the effect of several matrices on the PFU titration. Blood, bursa, spleen, trachea, and feather samples were collected from 6 SPF chickens (4 or 5 weeks old). The organ preparations were inoculated on CEF and the Innovax-ILT virus strain or the parental virus strain FC-126 was titrated afterwards, and the results compared. Only minor differences in all investigated organs could be observed.

Spread of the vaccine strain

The properties and possible spread of the Innovax-ILT vaccine strain to the naive target species chicken and several non-target species are examined in several studies.

The potential spread of Innovax-ILT vaccine strain HVT/ILT-138 to unvaccinated target animals (SPF chickens) and non-target animals (turkeys) was investigated with a 10-fold overdose using the recommended route of administration. The presence of the virus strain in vaccinated animals and sentinels was evaluated at 3 time points.

One group was composed of an equal number of vaccinated chickens and unvaccinated chickens as sentinels housed together. A second group was divided in vaccinated chickens housed together with the same number of unvaccinated turkeys. No spread to unvaccinated chickens was detected, but minor spread to turkeys was observed.

The potential replication and spread of the vaccine strain HVT/ILT-138 was evaluated in 4 potentially susceptible unvaccinated non-target species: turkeys, ducks, pheasants and quails (commercial birds). These are the potentially susceptible species most likely used for commercial purpose and housed in close proximity to the chicken sites.

The birds were vaccinated at 22 to 28 days of age and not at one-day-old. This should have no real impact as the first 4 weeks of life are known as the period in life in which animals are most susceptible. The setup of the study was discussed reasonably and was acceptable. Only female turkeys and ducks were used but as no differences in susceptibility between sexes are known, no impact on the results of the study is expected.

All birds were allocated per species into a vaccinated sub-group and an unvaccinated sub-group using equal numbers of animals. The vaccine was given at a 10-fold overdose. Birds were observed for 105 days except for the ducks which were observed only for 46 days as by this time no virus replication or spread could be detected. Only some spread from turkeys to turkeys could be demonstrated. Replication of the virus strain in vaccinated birds was observed in turkeys, pheasants and quails. No

clinical symptoms or macroscopic lesions related to the vaccine could be observed in any of the tested species.

In another study the replication in and the transmission to mice was examined as the non-target mammalian species with the highest potential of contact or closest proximity to the target species.

In this study mice were not brought into contact with vaccinated chickens but were vaccinated SC and housed together with unvaccinated sentinels. Administration of a 10-fold overdose of Innovax-ILT was compared to vaccination with a 10-fold overdose of the vaccine Nobilis Marexine CA126 containing the parental strain (HVT FC-126). Blood samples and spleen cell suspensions were examined for virus load 14 days post inoculation.

Replication of the virus could not be detected in any group. No clinical symptoms and pathological aberrations were observed. Therefore, mice seem to be refractory to this modified virus strain which is in line with the literature on the parental strain. In addition, a study to evaluate the susceptibility of mammalian cell lines was provided. The setup of the study, the relevance of the used mouse strain, the route of infection and the choice of time points and samples to re-isolate the virus strain have been discussed sufficiently and are acceptable.

Dissemination in the vaccinated animal

Passage MSV+4 of Innovax-ILT was used but only as single commercial dose ($10^{3.7}$ PFU/dose) and not at maximum titre ($10^{4.1}$ PFU/dose). Nevertheless, Innovax-ILT and the control vaccine Nobilis Marexine CA126) were used at the same titre, which is important for the assessment of comparability, and the virus strain has been isolated from all chosen samples.

One group of chickens was vaccinated with Innovax-ILT and the other group with Nobilis Marexine CA126 to compare the properties of both virus strains. No clinical symptoms related to the vaccination were observed and only unspecific minor signs could be detected. Furthermore, isolated white blood cells (WBC) and samples of 4 tissues (spleen, bursa, trachea, and feathers) were collected to re-isolate the virus strains. WBC isolation as required by Ph. Eur. monograph 0598 was conducted to show the presence of the virus in the peripheral blood. The choice of the examined organs is suitable, because the predilection sites of the viruses (HVT/ILTV) are covered and the route of transmission of the virus.

Results show that at the majority of time points the virus load of the organs is higher in the samples from birds vaccinated with the parent strain compared to the samples from birds vaccinated with Innovax-ILT. Most notable are the results from the feather samples as they show that the virus load of the samples from birds vaccinated with Nobilis Marexine CA126, the control product, is clearly higher than the samples from chickens vaccinated with Innovax-ILT.

In conclusion, no differences regarding tissue tropism could be observed compared to the parental strain.

Reversion to virulence of attenuated vaccines

Increase in virulence of the vaccine strain was investigated in two studies in accordance with Ph. Eur. monographs 5.2.6 and 0598. The test for increase in virulence is not recommended for HVT strains but is required for live recombinant vector vaccines to demonstrate that the insertion of foreign genes has not led to an increase in virulence or a modification in tissue tropism (EMEA/CVMP/004/04).

For the initial infection the vaccine was applied with a virus titre of $10^{4.8}$ PFU/dose which conforms to Ph. Eur. monograph 0589 which requires only a quantity of vaccine virus that will allow recovery of virus of the passages.

Fifteen (15) one-day-old SPF chicks per group were injected SC instead of intramuscularly (IM) to reflect the recommended route of administration for Innovax-ILT. Five (5) serial passages were conducted as required; for the last virus passage 30 birds were used. Natural spread of HVT is rarely seen in chickens so the virus was re-isolated from each passage in WBC and this WBC suspension was injected into the next group of chickens. The SC route was used for the following inoculations instead of the intraperitoneal (IP) route as this application route is more animal friendly and is as sensitive as the IP route. The presence of live virus could be demonstrated in each passage so the study is considered valid.

No clinical signs and no macroscopic lesions were observed in any passage of Innovax-ILT, therefore, it seems that the modified virus strain did not gain any virulence. It was noted that the mean plaques per dish rose in the 4th back passage but this can be regarded as a biological variation. The natural transmission per dander could not be demonstrated as HVT spreads only rarely between chickens.

For the required comparison of the 5th passage with the initial passage used for the reversion to virulence study, group 1 (5th back passage) and group 2 (10-fold overdose of MSV+4) were evaluated in the safety of one administration of an overdose study. No clinical signs related to the vaccine were developed during the observation period, but it was noticed that in a large number of birds of both groups unspecific clinical symptoms occurred. No differences are observed in the safety profile of the material used for the 1st passage compared to the 5th passage of the virus strain.

The results indicate that Innovax-ILT does not acquire virulence by sequential passaging through chickens.

Biological properties of the vaccine strain

No specific studies have been conducted to determine the intrinsic biological properties of the vaccine strain. However, in the other performed studies the vaccine strain did not cause clinical signs of MD or ILT in any of the vaccinated chickens.

The virus strain used for Innovax-ILT is based on the naturally apathogenic HVT FC-126 strain. The gD and gI genes of ILT virus have been inserted into the HVT genome. Both ILTV glycoprotein genes are present in the ILTV virion where gD is essential for cell entry and gI plays an accessory role in cell-to-cell spread. Several studies were performed to evaluate whether the insertion of these genes has changed the properties of the parent virus strain HVT FC-126.

In conclusion, the results of the provided studies indicate that no additional properties, apart from expressing the inserted ILTV glycoprotein genes, have been acquired in comparison to the parental strain.

Recombination or genomic reassortment of the strains

The probability of recombination or genomic reassortment with field or other strains shall be considered in line with the requirements of Directives 2001/82/EC and 2001/18/EC.

In virus strain HVT/ILT-138 used for Innovax-ILT, gD and gI genes of ILTV have been inserted into the parental strain HVT FC-126 genome. No gene deletions from the parental strain have been done. Regarding the potential for recombination of HVT/ILT-138 with vMDV or MDV vaccine strains, the risk

would be no greater than it is with currently available vaccines containing HVT. HVT is commonly present in vaccinated chickens that become "superinfected" with virulent MDV. Furthermore, serotype 3 HVT vaccines have been given with serotype 2 (SB-1) and/or serotype 1 (Rispens CVI988) MDV vaccine strains as a polyvalent vaccine for decades. There have never been reports on the recombination of HVT with either the virulent MDV or the serotype 2 or serotype 1 vaccine strains, hence this possibility can be considered as extremely small. The genome of HVT is not segmented; therefore, genomic reassortment cannot occur up to the current scientific knowledge.

The impact of a mixed application of an overdose Innovax-ILT with an overdose of Nobilis Rismavac has been evaluated in one laboratory study for 123 days. This combination of vaccines was also examined in other 2 field studies. No negative effects could be observed. In conclusion, the potential for recombination and genomic reassortment of the vaccine strain is considered negligible.

User safety

The applicant has provided a user risk assessment in accordance with the CVMP guideline for user safety for immunological veterinary medicinal products (EMEA/CVMP/IWP/54533/2006).

Innovax-ILT is a cell-associated live vaccine which contains the recombinant herpesvirus of turkeys strain HVT/ILT-138. In general, avian herpesviruses are not known to be a hazard to humans. HVT is not indicated in Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. The insertion of the glycoprotein genes of ILTV did not alter the biological properties of the strain and it has been shown in the previous studies that HVT/ILT-138 behaves like its parental HVT FC-126 strain and does not infect mammals.

Innovax-ILT contains no adjuvant, but the following excipients: basal medium, bovine serum and dimethyl sulfoxide (DMSO), and is diluted in solvent before administration. The DMSO present in the vaccine is listed in Table 1 of Commission Regulation (EU) No. 37/2010 with a no MRL required classification and is considered to be safe.

The solvent is an aqueous solution and contains potassium dihydrogen phosphate, sucrose, pancreatic digest of casein and phenolsulfonphthalein (phenol red) in water for injection. None of the ingredients poses a risk for the user and the solvent is already used for over 35 years.

The risk of an ampoule exploding when transferred from liquid nitrogen for thawing is estimated as very low and the consequence of potential cuts by the glass of the ampoule are estimated as medium (could lead to e.g. skin cut). The overall risk is therefore considered to be acceptable.

The potential risk for the user to be exposed to the vaccine during handling of the vaccine ampoule (skin contact) or as a result of self-administration is considered to be negligible.

The safety warnings are reflected in the SPC.

Study of residues

Not required.

The active ingredient being a substance of biological origin intended to produce active immunity does not fall within the scope of Regulation (EC) No. 470/2009 with regard to residues of veterinary medicinal products in foodstuffs of animal origin. In addition the other components of the vaccine are either listed in table 1 of the annex of Commission Regulation (EU) No. 37/2010 or considered as not falling within the scope of Regulation (EC) No. 470/2009 when used as in this product. The potential pharmacological activity of basal medium and of phenol red ingredients not covered by Regulation (EU)

No. 37/2010 has been addressed by the applicant and this is acceptable.

The withdrawal period is set at zero days.

Interactions

Mixing with Nobilis Rismavac

Please refer to the section on safety of the administration of an overdose study.

Concurrent use with live Newcastle disease vaccines

A study compliant with Ph. Eur. monograph 0450 was provided. Commercial batches were used to vaccinate one-day-old chicks. Four (4) groups of chickens were vaccinated with Innovax-ILT SC and with Nobilis ND C2 or Nobilis ND Clone 30 by eye drop on the same day or with Nobilis ND C2 or Nobilis ND Clone 30 alone. No clinical signs could be observed in any group. Therefore, the use of Innovax-ILT and Nobilis ND C2 or Nobilis ND Clone 30 at the same time at different sites is considered safe for one-day-old chicks. This is acceptable and appropriate information is presented in the SPC.

Field studies

Two (2) field studies are provided to investigate the safety of Innovax-ILT in the field: a first field study was carried out in the Netherlands and a second in the US to investigate the safety of simultaneous vaccination of layers with Innovax-ILT and Rismavac (US authorisation). In addition, a pharmacovigilance statement of Innovax-ILT for the period 2007 to 2013 for the countries where the vaccine is already registered was provided.

In the first field study 6,000 layer chickens were enrolled and the study was conducted according to good clinical practice (GCP) regulations. The study was blinded.

The chickens were divided into 2 groups: one group was vaccinated with a mixture of Innovax-ILT and Nobilis Rismavac, and the other group with the product Nobilis Rismavac+CA126 (containing MDV strain CVI-988 and HVT strain FC-126) according to the recommended vaccination scheme at 1-day of age. Representative commercial batches were used. Both groups showed a very low mortality over the whole observation period of 12 weeks and exhibited neither clinical signs nor pathologic lesions. No local reactions at the vaccination sites were observed except hematomas in some birds where blood vessels were injured and a proper advice has been included in the SPC. No significant difference was observed concerning the weight gain of both vaccination groups until the 12th week of life. Data on egg production are not available (but data of egg production comparison is provided in the 2nd field trial in the US). Information on the poultry farm and the vaccination schedule of the parenting flock are provided. In conclusion, the study demonstrates that Innovax-ILT mixed with Nobilis Rismavac is safe when administered in one-day-old layer chicks.

In the second field study a representative commercial batch of Innovax-ILT was used and was mixed with a batch of Rismavac (product authorized in US and corresponding to Nobilis Rismavac). The control group was vaccinated with RIS-MA (product authorized in US and corresponding to Nobilis Rismavac+CA126). Additionally, a standard vaccination programme for layer flocks was carried out. Results of examination of the both groups over 60 weeks indicate that no differences in mortality, morbidity, local reactions, feed intake and laying performance could be observed between both groups.

Pharmacovigilance statement of the use of Innovax-ILT in the field outside from the EU over a period of almost 6 years demonstrates that the vaccine showed no adverse reactions or lack of expected efficacy. The vaccine is already authorized in several countries.

Environmental risk assessment

An assessment of the potential risk to the environment from use of Innovax-ILT following the CVMP note for guidance on environmental risk assessment for IVMPs (EMEA/CVMP/074/95) was performed.

The vaccine strain HVT/ILT-138 has the capacity to spread to turkeys (natural host species of the parental strain FC-126). Spread to contact chicken could not be observed but it is known from literature that HVT can spread from chicken to chicken, although very poorly. Like for the parental strain it must be assumed that vaccinated chickens can shed the vaccine virus strain at low levels via feather follicle epithelium until the end of their life.
Survival and dispersal into the environment can only occur after vaccination from vaccinated chickens through virus present and released with epithelial cells from feather follicles. In order to replicate, virus in this feather dust will have to re-infect a permissive host via inhalation.

The likelihood that a hazard will occur is considered low as:

The virus spreads only poorly to other chickens and the chances of turkeys coming into contact with vaccinated chickens are low. In the unlikely event of a turkey being infected with the vaccine virus, the turkey could transfer the virus to a contact turkey and spread the vaccine virus. But taking into consideration that HVT is endemic and ubiquitous in domestic turkeys and the vaccine HVT strain, HVT/ILT-138, replicates and disseminates at a lower level, the likelihood of spread of the vaccine virus in turkeys is very low.

In case other avian species are infected with the vaccine strain, the consequences are negligible as the vaccine virus is apathogenic to avian species.

Innovax-ILT is already on the market outside the EU since 2007. No adverse reactions have been reported.

The studies on spread and dissemination of the vaccine do not indicate a change of the properties of HVT/ILT-138 in comparison to HVT FC-126. The excipients in Innovax-ILT are not different from the composition of other cell associated MD vaccines marketed by the company and like these other vaccines Innovax-ILT also does not have a toxic effect on the environment.

Taking all the risk factors into consideration, the level of risk to the environment of Innovax-ILT can be considered as negligible. Therefore, second phase evaluation is considered unnecessary. Based on the data provided, the environmental risk assessment can stop at Phase I. Innovax-ILT is not expected to pose a risk to the environment when used according to the SPC.

Environmental risk assessment (ERA) for products containing or consisting of genetically modified organisms (GMO)

The proposed vaccine Innovax-ILT is compliant with Directive 2001/18/EC.

Detailed information on the possible risks for humans and to the environment were provided. The parental HVT FC-126 strain as well as the recombinant HVT-ILT-138 strain does not infect humans and is restricted to the infection of avian species.

Innovax-ILT was generated by homologous recombination using a plasmid which contained the ILTV genes D and I, flanked by the HVT genome. The generation of the HVT/ILT-138 is described in more detail. The vaccine strain is genetically stable which has been tested by sequencing the inserts of MSV+4 and MSV+10.

The recipient virus HVT strain FC-126 is fully apathogenic and has been widely used for prevention of MD, and the applicant provided studies on replication, spreading, dissemination and reversion to virulence to support the persistent apathogenicity. Additionally, a safety study in mice has been provided to substantiate the retained host range restriction of Innovax-ILT.

The vaccine virus did not replicate in mice as a surrogate for mammals. It did replicate slightly in all chicken tissues tested, but slightly poorer in most tissues when compared to the recipient strain, which was most apparent in the feather follicles. Like for the parental HVT strain shedding occurs from vaccinated birds from the feather follicle epithelium. It is assumed that vaccinated chickens shed the vaccine virus at very low levels until time of slaughter and the vaccine strain may survive and disperse into the environment after vaccination. Stability of HVT strain in dust particles has not been determined under field conditions, but MDV has been shown to be stable at least for several months at room temperature. Virus replication had also been shown in non-target avian species (turkeys, pheasants, quail) but spreading occurred only from chicken to turkey as well as from turkey to turkey, not from chicken to chicken. After inoculation of an overdose in the target species the vaccine strain was apathogenic and no virulent properties could be observed. Accordingly, there may be some spread of the vaccine virus through dander into the environment.

Laboratory and field studies were carried out in combination with other MD vaccines and mixed use might pose a certain risk for recombination, because the vaccine viruses used are genetically very closely related, and they both persist in the target animal with shedding through feather dander.

More detailed information was provided on the stability of the vaccine virus in the environment. An additional expert opinion has been provided to estimate the risk of recombination of Innovax-ILT and Nobilis Rismavac with each other when delivered to chickens as a combined product and with other viruses that might be co-infecting chickens or be present in the environment, as well for Innovax-ILT to integrate into the chicken or turkey genome. The expert concludes that the risk of recombination is negligible.

The CVMP concluded that, taken together, any risk emerging from the use of the Innovax-ILT vaccine virus is negligible for humans and for the environment.

Overall conclusions on the safety documentation

The safety of Innovax-ILT at 10-fold overdose administered to one-day-old chicks by the SC route in 9 laboratory and 2 field studies was investigated in accordance with: Ph. Eur. monograph 0062 on vaccines for veterinary use; Ph. Eur. chapter 5.2.6 on evaluation of safety of veterinary vaccines and immunosera; Ph. Eur. monograph 0589 on MDV (live); Commission Directive 2009/9/EC amending Directive 2001/82/EC; and the regulations for genetically modified organisms (GMOs).

The vaccine did not cause clinical signs of MD or of ILT in any of the vaccinated chickens. No macroscopic or microscopic lesions attributable to the vaccine were observed. No negative influence on the development of the immune system could be observed. No studies were performed to investigate the repeated administration which is not relevant as the vaccination scheme stipulates only one administration at 1-day of age. However, accidental double vaccination on the same day is possible but seems to be a lesser burden than a 10-fold vaccination which proved to be safe.

Likewise, the examination of reproductive performance was not included and is not relevant for the vaccination scheme as the data of a field study and pharmacovigilance data from countries outside the EU where Innovax-ILT is already authorized do not indicate any possible damages.

The vaccine strain can be shed from vaccinated chickens via dander from 4 to at least 6 weeks post vaccination and spreads to contact turkeys. As spread to turkeys cannot be excluded, appropriate care should be taken to avoid direct or indirect contact between vaccinated chickens and turkeys. An appropriate warning has been included in the SPC. Spread to other avian species like pheasants, ducks and quails could not be detected; moreover, ducks seem to be refractory to the virus strain. Spread from chickens to mice (as example for spread to a mammalian species) was not demonstrated but seems to be very unlikely. Virus replication was neither observed in the vaccinated mice nor in the unvaccinated contact mice.

Dissemination of the vaccine virus strain has been shown in WBC, spleen, bursa cloacalis, and in the feather follicles. Feather follicles and spleen are prime locations of virus replication.

It can be concluded that the risk of reversion to virulence of the vaccine strain, in chickens is negligible. The biological properties of the parental strain seem to be unaltered after insertion of 2 glycoprotein genes and their regulatory elements of ILTV except for the expression of these 2 proteins.

The user safety has been adequately addressed. Appropriate warnings are included in the SPC.

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

The safety of Innovax-ILT and mixed administration with Nobilis Rismavac was tested in the laboratory (overdose study) and in the field. Performance and general health were similar between groups vaccinated with Innovax-ILT and/or with Innovax-ILT mixed with Nobilis Rismavac. Therefore, the mixed application of Innovax-ILT and Nobilis Rismavac is considered to be safe for one-day-old chicks. Adverse reactions associated with the vaccination were not observed.

The safety of the associated use (at the same day by different routes) of Innovax-ILT, Nobilis ND Clone 30 or Nobilis ND C2 was also demonstrated in an additional study.

Based on the data provided the ERA can stop at phase I. Innovax-ILT is not expected to pose a risk to the environment when used according to the SPC. Overall it is concluded that, the vaccine is considered to be safe.

Information concerning releases of GMO has been provided in appropriate studies. The final GMO has been shown to be genetically and phenotypically stable over 6 to 10 passages. The insertion of the foreign glycoproteins did not change the apathogenicity in the target species or other avian species or mammalians. Any risk emerging from the use of the Innovax-ILT vaccine virus is negligible for humans and has to be considered as low for the environment. More detailed information on stability of the vaccine virus in the environment and for the mixed use together with Nobilis Rismavac was provided.

Part 4 – Efficacy

Introduction and general requirements

Innovax-ILT is intended to provide immunity at 9 days post vaccination against MDV strains (like GA-5 and RB1B) and at 4 weeks post vaccination against ILTV strains (like LT-96-3). For earlier protection against very virulent MDV (vvMDV) strains (like RB1B), vaccines containing MDV strain CVI-988 and vaccines containing HVT strain FC-126 are commonly used together (mixed in one solvent bag before use).

To evaluate the protection against MD, efficacy of Innovax-ILT was evaluated by challenge both with vMDV (GA-5) and with vvMDV (RB1B), efficacy for Innovax-ILT mixed with Nobilis Rismavac by

challenge with vvMDV (RB1B). To evaluate the protection against ILT, efficacy of Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac was evaluated by challenge with ILTV strain LT-96-3.

Additional studies were presented for the use of Innovax-ILT in association with 2 vaccines against ND (Nobilis ND C2 and Nobilis ND Clone 30) at the same day and via different routes.

In these studies, protection against ND and protection against ILT were evaluated by challenge. An indirect estimation of the protection against MD was done on the basis of the level of protection achieved against ILT. Protection against ILT is dependent on the replication of the HVT/ILT-138 strain and the expression of the ILT gD and gI and it is expected that when a good protection against ILT is obtained, also a sufficient protection against MD will have been induced. An additional study was presented to demonstrate that there was no interference of the ND vaccines on the OOI for the MD protection of Innovax-ILT. This is acceptable.

Published literature was used as support for the DOI of the MD component to prove that protection after vaccination with HVT strains can be considered as lifelong. DOI for the ILT component of the vaccine was studied in a 60 weeks trial when animals were vaccinated with Innovax-ILT.

A field trial was performed to evaluate performance of the vaccine in the field. Birds were taken from the field and challenged in the laboratory both against ILTV and vvMDV.

Laboratory trials

As no specific Ph. Eur. monograph exists for a recombinant HVT virus vaccine that contains genes of ILTV and if the vaccine is intended to induce immunity to ILT and MD, the Ph. Eur. monographs 0589 (MDV, live) and 1068 (avian ILTV, live) have been consulted. Furthermore, for the associated use studies with ND vaccines the Ph. Eur. monograph 0450 (Newcastle disease vaccine, live) was considered.

Few deviations from Ph. Eur. monographs concerning MD and ILT were performed but are considered acceptable.

15 laboratory studies were carried out with Innovax-ILT.

Additional information is provided on the MD and ILT challenge strains (GA-5, RB1B, LT-96-3) concerning isolation, passage history and relevance. The efficacy examinations have been carried out in chickens by the recommended route of administration (subcutaneously) and at the youngest recommended age for vaccination (1 day) with the vaccine dose at the minimum titre ($10^{3.1}$ PFU).

For associated use studies on compatibility, standard vaccine doses were used. The influence of maternally derived antibodies (MDA) on the efficacy of the vaccine and the OOI has been evaluated.

All vaccine batches used in studies were prepared according to the manufacturing process described in part 2, except for the Innovax-ILT batch which was used in the DOI study for the ILTV component which has a slightly different composition.

Onset of immunity (OOI)

Three (3) studies were performed in one-day-old SPF chicks vaccinated with Innovax-ILT to investigate the dose response and the OOI against virulent and very virulent MDV infection.

Three (3) additional studies were carried out in one-day-old SPF chicks to investigate the dose response and OOI after vaccination with Innovax-ILT mixed with Nobilis Rismavac, 1 study for protection against very virulent MDV infection and 2 studies for protection against ILT infection (1

study for ILT had to be repeated).

MD component:

Efficacy of vaccination with Innovax-ILT applied via the SC route and OOI was determined in one-day-old SPF chicks by evaluation of protection against challenge with strain vMDV GA5 at 9 days post vaccination.

The setup of the challenge model fulfils the requirements of Ph. Eur. monograph 0589 (≥ 80% RPP) and a sufficient level of protection (RPP 87%) was reached. OOI for protection against vMDV after vaccination with Innovax-ILT at 9 days post vaccination as claimed is supported.

In an additional study, the efficacy and OOI for Innovax-ILT mixed with Nobilis Rismavac and applied via the SC route in one-day-old SPF chicks was determined by evaluation of protection against challenge with strain vvMDV (RB1B) at 5 days post vaccination.

The setup of the challenge model on the use of Innovax-ILT alone or mixed with Nobilis Rismavac fulfils the requirements of Ph. Eur. monograph 0589. The small deviation with the titre of Nobilis Rismavac, which is slightly above the minimum titre ($10^{3.2}$ PFU instead of $10^{3.0}$ PFU), is regarded acceptable as it is within the range of the test's variability.

The challenge with the vvMDV strain was valid. However, for animals vaccinated with Innovax-ILT only, the achieved protection level (RPP 66%) was not in line with the requirements of Ph. Eur.

Vaccination with Innovax-ILT mixed with Nobilis Rismavac resulted in protection levels (RPP 96%) which fulfil the requirements of Ph. Eur. monograph 0589 with regards to live MDV. The OOI of 9 days as claimed for the MD component of Innovax-ILT has been confirmed for the use of Innovax-ILT mixed with Nobilis Rismavac.

Based on the "classification of MDV in pathotypes" (Gimeno et al. 2008), a challenge study with strain GA-5 (vMDV) can be omitted when Innovax-ILT is mixed with Nobilis Rismavac.

Furthermore, the efficacy and OOI for Innovax-ILT applied via the SC route in one-day-old SPF chicks was determined by evaluation of protection against challenge with strain vvMDV (RB1B) at 9 days post vaccination.

The setup of the challenge model on the use of Innovax-ILT fulfils the requirements of Ph. Eur. monograph 0589. The challenge with the vvMDV strain was valid. Vaccination with Innovax-ILT resulted in protection levels (RPP 88.1%) which fulfil the requirements of Ph. Eur. monograph 0589 with regard to live MDV. The OOI at 9 days post vaccination as claimed for Innovax-ILT has been confirmed by challenge with vvMDV strain RB1B.

ILT component:

In the first study the efficacy and OOI for Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac and applied via the SC route in one-day-old SPF chicks has been evaluated with a dose below the claimed minimum titre for Innovax-ILT ($10^{2.8}$ PFU). The challenge with ILTV strain LT-96-3 at 4 weeks after vaccination was valid. A hundred percent (100%) of protection was reached in line with Ph.Eur. 1068 (≥ 90%) when animals were vaccinated with Innovax-ILT only. Vaccination with Innovax-ILT mixed with Nobilis Rismavac resulted in 75% protection. As compliance with Ph. Eur. monograph 1068 requirements could not be demonstrated when Innovax-ILT was mixed with Nobilis Rismavac, the study has been repeated.

In the repeated study the minimum dose for Innovax-ILT and lower doses for Nobilis Rismavac have been applied via the SC route. Time of challenge with strain ILT-96-3 was changed to 4 and 6 weeks instead of only 4 weeks post vaccination.

The setup of the challenge model on the use of Innovax-ILT or mixed with Nobilis Rismavac fulfilled the requirements of Ph. Eur. monograph 1068. The challenge with ILTV strain LT-96-3 was valid and protection levels (between 90 and 100%) in all vaccinated animals were achieved that fulfilled the requirements of Ph. Eur. monograph 1068, at 4 and 6 weeks post vaccination.

OOI of 4 weeks for the ILT component of Innovax-ILT is confirmed when animals are vaccinated with Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac.

The influence of maternal antibodies (MDA) on the efficacy of the vaccine

Four (4) studies were carried out in MDA-positive (MDA+) one-day-old commercial chicks to investigate the dose response and OOI after vaccination with Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac, 2 studies for protection against virulent vMDV and vvMDV and 2 studies for protection against ILT infection.

MD component:

The efficacy of Innovax-ILT or Innovax-ILT mixed with Nobilis Rismavac applied via the SC route in one-day-old MDA+ chicks was investigated in 1 study by evaluation of protection after challenge with vvMDV RB1B on day 9 post vaccination.

The influence of passively acquired and MDA on the efficacy of a vaccine has been adequately evaluated (Ph. Eur. monograph 5.2.7 on evaluation of efficacy of veterinary vaccines and immunosera); commercial batches for vaccination were used for this purpose.

Presence of MDA for MDV was confirmed by serology in hatch mates. Protection against Marek challenge in animals vaccinated with Innovax-ILT only and in animals vaccinated with Innovax-ILT mixed with Nobilis Rismavac is significantly higher compared to unvaccinated controls. Vaccination with Innovax-ILT mixed with Nobilis Rismavac fulfilled the protection requirements of Ph. Eur. monograph 0589 (RPP 92%). Vaccination with Innovax-ILT alone resulted in RPP of 46%.

In conclusion, in the presence of MDA the OOI of 9 days for the protection against MD is also confirmed by challenge with the vvMDV RB1B strain when Innovax-ILT is mixed with Nobilis Rismavac.

Another study was performed to address the efficacy of Innovax-ILT against a challenge with vMDV in birds with MDAs (against ILT + MD). Commercial birds were vaccinated with Innovax-ILT by SC route and challenged with vMDV strain GA5 on day 9 post vaccination. A statistically significant RPP of 66.6% was obtained. The results support the claim of Innovax-ILT for reduction of mortality, clinical signs and lesions also in MDA+ chickens.

ILT component:

The efficacy of Innovax-ILT or Innovax-ILT mixed with Nobilis Rismavac applied via the SC route in one-day-old MDA+ chicks was investigate one study by evaluation of protection after challenge with ITLV strain ILT-96-3 at 4 weeks post vaccination.

Presence of MDA for MDV and for ILT was confirmed by serology in hatch mates. Protection against ILT challenge in animals vaccinated with Innovax-ILT only and in animals vaccinated with Innovax-ILT mixed with Nobilis Rismavac is significantly higher compared to unvaccinated controls. Vaccination with Innovax-ILT alone resulted in 83 % protection, vaccination with Innovax-ILT mixed with Nobilis Rismavac in 63 % protection. The difference is not significant. It has to be stated that clinical signs in all vaccinated animals which were not protected are severe (animals died or were euthanized). In conclusion, Innovax-ILT is efficacious alone and mixed with Nobilis Rismavac in chickens with MDA against both HVT and ILT when challenged with virulent ILT virus at 4 weeks post vaccination and OOI

for the ILT component of Innovax-ILT is confirmed.

A second study was performed to demonstrate efficacy of Innovax-ILT mixed with Nobilis Rismavac applied via the SC route in one-day-old MDA+ chicks by evaluation of protection after challenge with ITLV strain ILT-96-3 at 6, 10 and 12 weeks post vaccination.

Presence of MDA for ILT was confirmed by serology in hatch mates. Four-weeks-old SPF controls were used as challenge controls due to possible age resistance against ILTV challenge with strain LT-96-3. Age matched control MDA+ chickens (vaccinated with Nobilis Rismavac+CA126) were not fully sensitive to infection with virulent ILTV.

In animals vaccinated with Innovax-ILT and Nobilis Rismavac and challenged at 6, 10 and 12 weeks post vaccination significantly better protection levels when compared to the SPF challenge controls were achieved at 10 and 12 weeks post vaccination when compared to the MDA+ controls. At 6 weeks post vaccination no significant difference was observed between the Innovax-ILT and Nobilis Rismavac vaccinated group compared to the MDA+ control chickens (vaccinated with Nobilis Rismavac+CA126) partly based on the above mentioned low sensitivity of the control MDA+ chickens for ILT infection. It must be stated that in challenge at 6 weeks post vaccination absolute protection in the group which was vaccinated with Innovax-ILT mixed with Nobilis Rismavac (65%) is comparably low and severe signs of disease are seen in unprotected vaccinated animals. In conclusion, limited protection to ILT is seen in the presence of MDA and this point has been reflected in the SPC.

Duration of immunity (DOI)

MD component:

It is accepted that the immunogenicity of the HVT part of Innovax-ILT is comparable to the immunogenicity of the parental HVT strain. As the immunogenicity of HVT is accepted to be lifelong there is no need to perform another study to demonstrate the DOI for the protection against MD after vaccination with Innovax-ILT. In can be concluded that DOI of the MD part of Innovax-ILT is lifelong.

ILT component:

The DOI of vaccination with Innovax-ILT against ILT infection when administered via the SC route was investigated in one study by evaluation of protection after challenge with ILTV strain ILT-96-3 at 10, 20, 30, 40, 50 and 60 weeks of age.

The setup of the challenge model on the use of Innovax-ILT fulfils the requirements of Ph. Eur. The challenge with ILTV strain LT-96-3 was valid at all times if 4-weeks-old unvaccinated SPF chickens are used as challenge controls. Using older animals, challenge was not valid at each time point of the challenge, possibly due to age resistance against ILT.

In comparison to the 4-week-old SPF controls, protection levels against ILT for all animals vaccinated with the minimum dose ($10^{3.1}$ PFU) were in line with the requirements of Ph. Eur. at all times of challenge (≥ 90% protection).

If the vaccinated animals are compared to controls of the corresponding age to each challenge group, the difference in protection between animals vaccinated with the minimum dose and controls is not found to be significant in all vaccinated groups at 10, 40 and 50 weeks of challenge. This was due to the low prevalence level in the age-matched control. This can be partially due to the change of batches and titres of challenge material between different times of challenge. In the challenge study 60 weeks post vaccination, which is the claimed DOI, significant difference in protection is demonstrated between all vaccinated groups and controls. In conclusion, DOI of the ILT part of Innovax-ILT is

supported at 60 weeks.

Additional studies – compatibility studies

The following studies were performed to examine the use of Innovax-ILT mixed with Nobilis Rismavac:

MD component:

OOI for Innovax-ILT mixed with Nobilis Rismavac after SC administration was evaluated in one-day-old SPF chicks by evaluation of protection against vvMDV (RB1B) challenge. (See also section "onset of immunity (OOI)").

Two (2) groups of one-day-old commercial layers after SC administration of Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac has been determined by challenge in the laboratory with vvMDV (RB1B) virus 9 days post vaccination under field conditions (see also section "The influence of maternal antibodies (MDA) on the efficacy of the vaccine").

For associated use of vaccines (here: mixed before administration) OOI and DOI have to be confirmed for all involved vaccines and antigens (EMA/CVMP/IWP/594618/2010). OOI of 9 days as claimed regarding the MD part of the vaccine has been shown for SPF animals and for MDA+ chickens.

When Innovax-ILT is mixed with Nobilis Rismavac, DOI for the entire risk period (about 60 weeks) has not been shown for the MD part of the vaccine. Based on the comparable results achieved in the vvMDV (RB1B) challenge at 9 days after vaccination in SPF animals whether they are vaccinated with Innovax-ILT or with the parental HVT strain, it is accepted that the protective potential of both strains including their ability to induce lifelong immunity is identical. As there is no evidence that they negatively influence each other, DOI for the entire risk period can be presumed for the protection against MD after vaccination with Innovax-ILT.

ILT component*:*

The OOI for Innovax-ILT alone and Innovax-ILT mixed with Nobilis Rismavac was evaluated in two studies in one-day-old SPF chicks after SC administration by evaluation of protection against ILT challenge.

The evaluation of protection has been repeated using a different dose and additional time of challenge (see also section "onset of immunity (OOI)").

Further studies have been performed to show the efficacy of Innovax-ILT alone and Innovax-ILT mixed with Nobilis Rismavac after SC administration in one-day-old MDA+ chicks at 4 weeks post vaccination and at 6, 10 and 12 weeks post vaccination (see also section "The influence of maternal antibodies on the efficacy of the vaccine").

When Innovax-ILT is mixed with Nobilis Rismavac, OOI for the ILT part of Innovax-ILT is confirmed to be 4 weeks as claimed for SPF chickens and also with some limitations for MDA+ animals. DOI for 12 weeks has been shown when Innovax-ILT is mixed with Nobilis Rismavac in MDA+ animals.

DOI for 43 weeks for the ILT part of the vaccine after vaccination with Innovax-ILT mixed with Nobilis Rismavac has been demonstrated by a challenge study. In this study, commercial layers were vaccinated in the field at 1 day of age by the SC route with one dose of Innovax-ILT mixed with one dose of Rismavac. At 42-weeks-old, 30 of the commercial layers were transported to Purdue University for an ILT challenge at 43 weeks of age. For the challenge the standard USDA ILTV challenge virus strain was used.

The used challenge strain has been justified to be relevant to the European epidemiological situation. Even if the study has not been performed completely in compliance with the requirements of Ph. Eur. (MDA+ animals were used, anyway), results sufficiently support the DOI for the protection against ILT after vaccination with Innovax-ILT when mixed with Nobilis Rismavac.

Additional supportive information for the DOI of the ILT component of Innovax-ILT when mixed with Nobilis Rismavac has been obtained from the field trial performed in the USA. Considering the serological data, it can be concluded that the DOI for the protection against ILT is not affected when Innovax-ILT is used in combination with Nobilis Rismavac.

The following studies were performed to support the use of Innovax-ILT at the same day by different routes with Nobilis ND C2 or Nobilis ND Clone 30 in SPF chickens:

ILT component:

A study was performed to demonstrate the efficacy of Nobilis ND C2 and Nobilis ND Clone 30 when used on the same day (different routes) with Innovax-ILT by evaluation of protection against ILT challenge at 4 weeks post vaccination.

Innovax-ILT was given subcutaneously whereas Nobilis ND C2, Nobilis IB MA5+Clone 30 and Nobilis IB 4/91 were given ocularly.

The challenge was not valid according to the scoring as detailed in chapter "setup of a challenge model" (83% ILT positive animals instead of 90% as required by Ph. Eur.). Validity depends on the scoring of only one animal, which shows clinical signs to an extend leading nearly to a positive scoring.

Results showed that in all groups vaccinated with Innovax-ILT >90% protection against ILT challenge at 4 weeks was obtained independent of the combination with the mentioned ND or infectious bronchitis (IB) vaccines. For associated use of vaccines (here: use at the same day but by different routes) OOI and DOI have to be confirmed for all involved vaccines and antigens (EMA/CVMP/IWP/594618/2010). By the above study, OOI against ILT challenge is demonstrated at 4 weeks.

Regarding efficacy of the other vaccines, the efficacy of the IB parts of Nobilis IB 4/91 and Nobilis Ma5+Clone 30 has not been proven by challenge as only use of Innovax-ILT at the same day with Nobilis ND Clone 30 and Nobilis ND C2 is claimed.

In conclusion, the OOI for protection against ILT at 4 weeks post vaccination will not be affected by the mentioned ND vaccines.

MD and ILT component:

OOI (and DOI) against MD (and ILT) after vaccination with Innovax-ILT when given concurrently with Nobilis ND C2 or with Nobilis ND Clone 30 was investigated in an additional study.

To show appropriate replication of HVT when Nobilis ND C2 or Nobilis ND clone 30 are used in association with Innovax-ILT, 3 groups of one-day-old SPF chicks were respectively vaccinated with Innovax-ILT, with Innovax-ILT and Nobilis ND C2 or with Innovax-ILT and Nobilis ND Clone 30. Innovax-ILT was given via SC route, the ND vaccines via ocular route. The spleen was harvested at 7 days post vaccination and the viraemia was determined.

One hundred percent (100%) viraemia in all vaccinated birds could be demonstrated at 7 days post vaccination, leading to the conclusion that no detectable interference of the ND vaccines on the initial infection with the Innovax-ILT vaccine takes place at this time. Therefore, the OOI for protection against MD at 9 days post vaccination will not be affected by the mentioned ND vaccines.

The DOI for the HVT and ILT part of Innovax-ILT can be justified by showing that there is no interference observed at the initial infection and replication of the HVT virus in the vaccinated birds. Once infection is established, the HVT virus will persist providing lifelong DOI for both the ILT and the HVT component. Therefore, the OOI experiment can be considered to be predictive for the DOI immunity elicited by both the ILT and HVT component of this vaccine.

In conclusion, the OOI for protection against MD at 9 days post vaccination is not affected by the mentioned ND vaccines. The DOI for the MD part of Innovax-ILT will persist lifelong.

ND components (from Nobilis ND C2 and Nobilis ND Clone 30):

Efficacy of Nobilis ND C2 and Nobilis ND Clone 30 when used on the same day (different routes) with Innovax-ILT was evaluated in a challenge study against ND with NDV strain Herts 33/56 at day 22 post vaccination.

The challenge was valid according to the requirements of Ph. Eur. and guideline EMA/CVMP/IWP/594618/2010.

In all ND vaccinated groups 100% protection against ND challenge was obtained independent of the combination with Innovax-ILT. No protection was observed in unvaccinated SPF controls. Innovax-ILT and Nobilis ND Clone 30 or Nobilis ND C2 can be administered at one day of age without affecting ND efficacy at day 22.

No study on DOI for application of Innovax-ILT and Nobilis ND Clone 30 or Nobilis ND C2 on the same day was performed as the occurrence of interferences is considered unlikely. This approach is acceptable.

The OOI for Nobilis ND Clone 30 (3 weeks) when used alone or associated with Innovax-ILT is demonstrated by challenge at day 22 post vaccination. To demonstrate the OOI for Nobilis ND C2 (2 weeks) when it is used associated with Innovax-ILT, the immunity study of the original Nobilis ND C2 dossier was used and a new study to compare OOI when Nobilis ND C2 is used alone or in association with Innovax-ILT by challenge with NDV strain Herts 33/54, 2 weeks post vaccination was presented. Innovax-ILT was given via SC route, Nobilis ND C2 vaccines via ocular route.

The setup of the new challenge model on the use of Innovax-ILT fulfils the requirements of Ph. Eur. The challenge with the NDV strain was valid.

In both studies the achieved level of protection was similar to the protection achieved for animals vaccinated with Nobilis ND C2 only.

In conclusion, it was shown that the OOI of Nobilis ND C2 and Nobilis ND Clone 30 is not negatively affected by the associated use of Innovax-ILT.

Field trials

In the field trial, standard vaccine dose was used. The field trial has been conducted according to the principles of GCP.

The study was performed to examine the efficacy of Innovax-ILT in the field (see also safety part C).

Mortality was low, no disease related symptoms were observed and the condition of the chickens was good throughout the trial, indicating vaccine efficacy.

Chickens were taken from the field trial and challenged in the laboratory to demonstrate protection after vaccination under field conditions in two studies (see also section "The influence of maternal

antibodies (MDA) on the efficacy of the vaccine.").

In the first challenge study, the efficacy of the vaccination with Innovax-ILT alone and Innovax-ILT mixed with Nobilis Rismavac was examined by evaluation of protection after challenge under laboratory conditions with vvMDV. Animals were significantly protected post vaccination with either Innovax-ILT alone or Innovax-ILT mixed with Nobilis Rismavac.

In the second challenge study, the efficacy in the field of the vaccination with Innovax-ILT alone and Innovax-ILT mixed with Nobilis Rismavac was also examined by evaluation of protection after challenge under laboratory conditions with ILTV. Animals did show varying levels of protection post vaccination with either Innovax-ILT alone or Innovax-ILT mixed with Nobilis Rismavac. The level of protection in general was higher when Innovax-ILT was given alone. When Innovax-ILT was applied mixed with Nobilis Rismavac, the development of immunity towards ILT was delayed up to 10 weeks post vaccination. This possible delay is mentioned in section 4.8 of the SPC.

Overall conclusion on efficacy

The efficacy claims were evaluated in several laboratory and field efficacy studies.

The immunogenicity tests of the presented efficacy trials are performed in compliance with Ph. Eur. monograph 0589 on MDV (live), Ph. Eur. monograph 1068 on avian ILTV (live) and Ph. Eur. monograph 0450 on Newcastle disease vaccine (live) with a few deviations regarding the criteria for classification of MD positive animals, the time of challenge for ILT, and the use of unvaccinated controls that were considered acceptable.

Efficacy of Innovax-ILT in protection against ILTV infection:

The efficacy of vaccination with a minimum dose of Innovax-ILT in one-day-old SPF chicks via the SC route was investigated by challenge with virulent ILTV strain LT-96-3. OOI is demonstrated at 4 weeks post vaccination and DOI is established at 60 weeks post vaccination for the ILT part of the vaccine.

For associated use of vaccines, OOI and DOI have to be confirmed for all involved vaccines and antigens (EMA/CVMP/IWP/594618/2010).

Concerning the associated use of Innovax-ILT with Nobilis Rismavac, OOI at 4 weeks post vaccination was demonstrated. However, a lower protection in MDA+ chickens was shown when Innovax-ILT is combined with Nobilis Rismavac than when used alone. This point is reflected in the SPC.

DOI was confirmed under these circumstances.

Concerning the associated use of Innovax-ILT with Nobilis ND C2 and Nobilis ND Clone 30, at the same time by different route of administration, OOI and DOI concerning ILT were confirmed.

Moreover, protection against NDV (strain Herts 33/56) was demonstrated at 22 days post vaccination confirming the OOI for Nobilis ND Clone 30 (3 weeks) when it is used associated with Innovax-ILT. It has been also demonstrated that OOI for Nobilis ND C2 is 2 weeks if Innovax-ILT is given at the same day. It is accepted that no study on DOI for Nobilis ND Clone 30 and Nobilis ND C2 is performed when used at the same day with Innovax-ILT.

In conclusion, it was shown that the OOI of Nobilis ND C2 and Nobilis ND Clone 30 is not negatively affected by the concurrent use of Innovax-ILT.

In presence of MDA, OOI against ILT was demonstrated at 4 weeks post vaccination, in animals vaccinated with Innovax-ILT. When Innovax-ILT was mixed with Nobilis Rismavac, the development of

immunity towards ILT was delayed in one study. This possible delay is mentioned in section 4.8 of the SPC.

Efficacy of Innovax-ILT in protection against MDV infection:

The efficacy of vaccination with a minimum dose of Innovax-ILT in one-day-old SPF chicks via the SC route was investigated by challenge with virulent MDV GA5 and vvMDV RB1B. OOI is demonstrated at 9 days post vaccination for the MD part of the vaccine. Reduced, but still significant protection against challenge with the vvMDV (strain RB1B) could be observed in animals vaccinated with Innovax-ILT and challenged at day 5 post vaccination. OOI at 5 days for protection against MD can be achieved when Innovax-ILT is mixed with Nobilis Rismavac as shown by protection against challenge with vvMDV (strain RB1B). This has been reflected in the SPC and product literature.

The DOI for the HVT part of the vaccine is regarded as justified. Comparability of both the HVT part of Innovax-ILT and the parental HVT strain has been sufficiently supported. Lifelong immunity for the parental HVT strain is accepted therefore it is also accepted for Innovax-ILT.

Concerning the associated use of Innovax-ILT with Nobilis Rismavac, OOI was demonstrated in one-day-old SPF chicks against challenge with the vvMDV strain (RB1B) at 5 days post vaccination. A challenge with strain GA-5 (vMDV) has not been performed to show protection of vaccination with Innovax-ILT mixed with Nobilis Rismavac, which has been justified by citation of serotype 1 classification by OIE.

In one-day-old MDA+ animals, OOI was demonstrated at 9 days after vaccination. DOI was not demonstrated as both herpes virus strains induce lifelong immunity and there is no evidence that both strains negatively influence each other. This is acceptable.

Concerning the associated use of Innovax-ILT with Nobilis ND C2 and Nobilis ND Clone 30, administered at the same time by different route, the OOI of the MD part of Innovax-ILT is confirmed at 9 days post vaccination and the DOI is confirmed to be provided lifelong. The conclusions concerning protection against ND already presented above (under the ILT section).

In presence of MDA, the OOI of Innovax-ILT and Innovax-ILT mixed with Nobilis Rismavac was demonstrate at 9 days post vaccination in one-day-old MDA+ chicks against vvMDV and vMDV. Full protection was achieved in animals vaccinated with Innovax-ILT mixed with Nobilis Rismavac against vvMDV (challenge with vMDV was not performed as it is unlikely that challenge with a less virulent virus strain will yield different results).

Part 5 – Benefit-risk assessment

Introduction

Innovax-ILT is a live recombinant vaccine based on the naturally avirulent turkey herpesvirus strain HVT FC-126 expressing the gD and gI of infective laryngotracheitis virus (ILTV).

Innovax-ILT is intended for use for the prevention of MDV and ILTV infections in chickens. These viruses are circulating worldwide and cause MD and infective laryngotracheitis (ILT). Both diseases affect the global chicken industry by causing losses in production of chickens and chicken products.

MD is a common lymphoproliferative disease of chickens characterized by mononuclear cellular infiltrates in peripheral nerves and various organs and tissues. Several clinical and pathological syndromes may develop after infection with MDV: lymphoproliferative syndromes like lymphomas and

nerve lesions, fowl paralysis, skin leucosis and ocular lesions; lymphodegenerative syndromes like early mortality syndrome, cytolytic infection, immunodepression; central nervous system syndromes like transient paralysis, persistent neurological disease, and vascular syndromes like atherosclerosis.

The acute tumorous form can cause mortality rates of up to 50% whereas in the classical neurological form mortality rarely exceeds 15%. Chickens become infected at an early age via inhalation of dander containing virus which can remain infectious for several months in the environment. MDV-infected birds can be carriers and shedders of the virus for life.

ILT is an infection of the respiratory tract in chickens which may also cause performance losses and decreased egg production. Two (2) forms of ILT are recognized, the mild and the severe ILT form. Clinical signs associated with the mild form include conjunctivitis, swelling of the sinuses, watery eyes, nasal discharge and mild tracheitis with a very low mortality. The severe form is marked by symptoms like coughing, gasping, marked dyspnoea, respiratory depression, expectorations of blood stained mucus associated with high morbidity (90-100%) and variable mortality rates (5-70%). The virus can be latently present in a low percentage of chickens of an infected flock and might reappear during a period of stress.

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

Benefit assessment

Direct therapeutic benefit

Well conducted and controlled clinical trials demonstrated that the product is efficacious to reduce mortality, clinical signs and lesions due to infection with avian ILTV and MDV in chickens vaccinated at 1 day of age by SC injection.

Data on the associated use of Innovax-ILT with Nobilis Rismavac, Nobilis ND Clone 30 or Nobilis ND C2 respectively, are provided.

OOI was established against ILTV infection at 4 weeks after vaccination and against MDV infection at 9 days after vaccination.

DOI was established against ILTV infection for 60 weeks after vaccination. No data are provided for the DOI against MDV infection and this is acceptable as the HVT virus produces a persistent infection providing a lifelong immunity.

OOI and DOI have been confirmed for Innovax-ILT in presence of MDA.

Concerning compatibility of Innovax-ILT when used mixed with Nobilis Rismavac an OOI of 5 days has been demonstrated for MD and has been confirmed at 4 weeks for ILT in SPF animals.

When Innovax–ILT is mixed with Nobilis Rismavac the development of immunity towards ILT may be delayed in animals with MDA.

OOI for MD and ILT has also been confirmed when Innovax-ILT is administered with Nobilis ND C2 or Nobilis ND Clone 30 at the same day by different routes in SPF chickens.

Additional benefits

The product gives the possibility to vaccinate one-day-old chicks against ILTV infection. Currently, only vaccination from 4 weeks of age onwards is possible.

Risk assessment

The main potential risks are identified as follows:

Quality:

The formulation and manufacture of Innovax-ILT is well described and specifications set will ensure that product of consistent quality will be produced provided that conditions are fulfilled.

For the target species:

The product is generally well tolerated in the target animal. No adverse reactions were observed after a tenfold overdose of Innovax-ILT by the SC route. The vaccine is based on an apathogenic vaccine strain, which is shown to be safe for chickens. Vaccination has to be done with care as trauma of the blood vessels in the neck is possible and this is reflected in the SPC. Reversion to virulence after 5 serial passages in chickens could not be demonstrated.

The efficacy of the product when used mixed with Nobilis Rismavac regarding the protection against ILT was observed to be delayed in presence of MDA and this is reflected in the product information.

For the user:

The user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

The vaccine is filled in glass ampoules and stored in liquid nitrogen and appropriate precautions and warnings for safe handling of the ampoules are included in the SPC.

For the environment:

The vaccine virus is shed by the feather epithelium and the infected dander can persist in the environment. It was demonstrated that spread to turkeys is possible. No spread to chickens was observed but cannot be excluded.

Mixing of Innovax-ILT with Nobilis Rismavac to prevent infection with very virulent MDV strains has been proposed. The possible recombination of the GMO organism with MDV strain Rispens CVI988 included in Nobilis Rismavac is negligible.

For the consumer:

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

Risk management or mitigation measure

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

Evaluation of the benefit-risk balance

The product has been shown to be efficacious to induce active immunization in chickens to reduce mortality, clinical signs and lesions of MD and ILT. The formulation and manufacture of Innovax-ILT is adequately described and set specifications will ensure that a finished product of consistent quality will be produced. Innovax-ILT is well tolerated by the target animals and presents an acceptable risk for

users when used as recommended and appropriate warnings have been included in the SPC. The withdrawal period is set at zero days.

The product has been shown to have an overall positive benefit-risk balance.

Conclusion on benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and product literature.

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 Innovax-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).

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Innovax–ILT.