18 April 2024
EMA/220147/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Respivac TRT (current name: Respivac aMPV) (EMEA/V/C/006160/0000)

Vaccine common name: Turkey rhinotracheitis virus, live

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Introduction

The applicant Laboratorios Hipra, S.A. submitted on 31 January 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Respivac TRT (the name was changed into Respivac aMPV, via variation, before the publication of this EPAR), through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**).

The eligibility to the centralised procedure was agreed upon by the CVMP on 14 July 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

At the time of submission, the applicant applied for the following indication:

"Active immunisation of chickens to reduce the respiratory signs caused by virulent avian metapneumovirus."

Each dose of Respivac TRT contains $10^{1.8}$ – $10^{5.4}$ $CCID_{50}$ of live avian metapneumovirus subtype B, strain 1062, as active substance. It is intended for chickens and is presented in packs with 1 vial or 10 vials of 10 ml containing 1,000 doses, 2,000 doses, 5,000 doses, or 10,000 doses of lyophilisate.

The rapporteur appointed is Esther Werner and the co-rapporteur is Christine Miras.

The dossier has been submitted in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

On 18 April 2024, the CVMP adopted an opinion and CVMP assessment report.

On 30 May 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Respivac TRT.

Scientific advice

Not applicable.

Limited market status

Not applicable.

Part 1 - Administrative particulars

Summary of the Pharmacovigilance System Master File

The applicant has provided a summary of the pharmacovigilance system master file, which fulfils the requirements of Article 23 of Commission Implementing Regulation (EU) 2021/1281. Based on the information provided the applicant has in place a pharmacovigilance system master file (PSMF) has the services of a qualified person responsible for pharmacovigilance and has the necessary means to fulfil the tasks and responsibilities required by Regulation (EU) 2019/6.

Manufacturing authorisations and inspection status

Active substance

Manufacture and primary packaging of the active substance take place at LABORATORIOS HIPRA, S.A., Amer, 17170 (Girona), Spain.

A GMP declaration for the manufacturing site mentioned above was provided by the Qualified Person (QP) at that site. The declaration was based on an on-site audit, which has taken into consideration the GMP certificate available for the active substance site issued by the Spanish competent authority AEMPS following inspection.

The site has a manufacturing authorisation issued on 28/11/2022 by AEMPS (Spain).

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued by AEMPS on 30/11/2022, referencing an inspection on 22/07/2022.

Finished product

Vaccine bulk formulation and primary packaging of the vaccine take place at LABORATORIOS HIPRA, S.A., 17170 (Girona), Spain.

Quality control testing, secondary packaging and batch release (certification) of the vaccine take place at LABORATORIOS HIPRA, S.A., Amer, 17170 (Girona), Spain.

A GMP declaration for the manufacturing sites above was provided by the Qualified Person (QP). The declaration was based on an on-site audit, which has taken into consideration the GMP certificate available for the active substance site issued by AEMPS (Spain) following inspection.

A manufacturing authorisation for the manufacturing sites was issued on 28/11/2022 by AEMPS.

A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued by AEMPS on 30/11/2022, referencing an inspection on 22/07/2022.

Overall conclusions on administrative particulars

The summary of the pharmacovigilance system master file is considered to be in line with legal requirements.

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

Part 2 - Quality

Quality documentation (physico-chemical, biological, and microbiological information)

Qualitative and quantitative composition

The vaccine is presented as a lyophilisate for suspension for oculonasal use (by spray administration)

or use in drinking water and contains live avian metapneumovirus (aMPV) subtype B, strain 1062, at a titre of 1.8 – 5.4 $\log_{10}$ $CCID_{50}$/dose as active substance. The vaccine contains no adjuvant. Other ingredients are dextran, sucrose, gelatine, NZ amine, sorbitol, potassium dihydrogen phosphate and dipotassium phosphate.

The product is available in multidose presentations containing 1,000, 2,000, 5,000 or 10,000 doses/vial.

Container and closure system

The vaccine is filled into colourless type I glass vials in accordance with the European Pharmacopoeia (Ph. Eur.) 3.2.1. The vials are closed with bromobutyl rubber stoppers in accordance with Ph. Eur. 3.2.9 and sealed with aluminium caps. The specifications and certificates demonstrating Ph. Eur. compliance for the vials and the stoppers are included in the dossier. A satisfactory certificate of analysis (CoA) of the aluminium caps has been provided. Although the stopper will not be penetrated with a needle for opening of the multi-dose vaccine vials, a self-sealing test confirmed appropriate self-sealing properties.

The sterilisation processes of containers and closures are adequate and performed in accordance with pharmacopeial requirements.

The process of vial opening and vaccine reconstitution is described in sufficient detail.

Product development

Introduction

Infection of turkeys and chickens with aMPV or avian rhinotracheitis virus (TRT) is associated with both economic and animal welfare problems. The main problem are not the symptoms of the acute, highly contagious upper respiratory tract disease, which are often mild, but the increased susceptibility of the infected chickens for infection by secondary pathogens.

The frequency and control of aMPV infections on poultry farms is highly dependent on the management practices including the implementation of general hygiene principles and vaccination strategies. Respivac TRT has been developed in order to protect chickens against aMPV infection from the first days of age by spray vaccination or vaccination in drinking water.

Choice of the active substance

Vaccine strain 1062 has been chosen based on its safe and efficacious use in already authorised vaccines for the control of aMPV infections in poultry farms. The reversion to virulence study confirmed the stable attenuation of the virus. The referenced scientific literature further supports the stable attenuation and safe use as vaccine virus.

The epidemiological relevance of the selected vaccine strain is justified since it belongs to the same aMPV subtype (i.e. B subtype) as the most prevalent strains observed in field infections across Europe. In addition, the observed reduction of respiratory signs after vaccination with Respivac TRT and challenge with a recent field isolate (also of B subtype) in the efficacy studies support the suitability of the chosen strain.

A detailed description on the history of the vaccine strain is included in the quality part of the dossier.

Excipients

The vaccine is composed of the active substance and the freeze-drying excipient without any

adjuvant. The development of the complex freeze-drying excipient is the main improvement in comparison to other authorised live vaccines and has been developed in order to ensure the stability, viability and immunogenicity of the virus during and after the lyophilisation. The excipient contains dextran, sucrose, gelatine, sorbitol, potassium dihydrogen phosphate, dipotassium phosphate and NZ amine.

Overages

The minimum effective titre determined in the efficacy studies is 1.8 $\log_{10}$ $CCID_{50}$/dose. A higher specification has been defined for release, adequately justified. The maximum titre of 5.4 $\log_{10}$ $CCID_{50}$/dose has been satisfactorily justified.

Packaging

The primary packaging consists of type I glass vials (Ph. Eur. 3.2.1), bromobutyl rubber stoppers (Ph. Eur. 3.2.9) and aluminium caps. The high quality of the vials and stoppers is appropriate for the materials to remain unaffected during the extreme conditions of the lyophilisation process.

Manufacturing process

The manufacturing process follows the GMP requirements and it is based on a seed lot system for the aMPV viral antigen and VERO cells used for virus propagation. The working seed virus is passaged in cell culture bottles for the preparation of the pre-inoculum and the inoculum. The inoculum is used for production of the antigen batch in a bioreactor equipped with VERO cells attached to microcarriers. The media used are supplemented with antimicrobials. Satisfactory information, confirming that only trace amounts below the established maximum residue limits (MRLs) of these antimicrobial substances will be present in the final vaccine, is provided. After harvest and concentration, the viral antigen and the freeze-drying excipient are consistently blended. The vaccine is then filled in the vials and subjected to the lyophilisation process. All stages are conducted under aseptic conditions and follow GMP requirements. To minimise the risk of microbial contamination of the vaccine, further measures, such as sterile filtration of the antigen batch and sterilisation of the freeze-drying excipient before blending, are in place. For release, all batches must pass the validated test for sterility (Ph. Eur. 2.6.1).

Description of the manufacturing method

The manufacturing process is divided into the manufacture of the antigen followed by the production of the finished product.

The manufacturing process of the aMPV strain 1062 follows conventional processes for virus propagation on cells and has been described in sufficient detail. VERO cells, a primate renal fibroblast-like cell line, are propagated until sufficient VERO cells are produced. Details on the upscaling process and the passaging, such as the split ratio for passaging and details on the trypsinisation procedure for cell harvest, have been provided. The number of cell passages from the working seed cells (WSC) to the passage used for virus infection complies with the requirements of Ph. Eur. 0062.

The working seed virus is passaged in cell culture bottles for the preparation of the pre-inoculum and the inoculum. The inoculum is used for production of the antigen batch in a bioreactor equipped with VERO cells attached to microcarriers. The final antigen batch is obtained after concentration of the harvest. Adequate description has been provided of validated storage periods and temperature ranges at different stages of the process. At each step of the manufacturing process, a test for sterility and viral titre is performed.

Satisfactory information on the preparation of the freeze-drying excipient by dissolution of the

individual ingredients followed by sterilisation by a validated process, is provided. The freeze-drying excipient may be stored until blending. Appropriate validation storage of the freeze-drying excipient is also provided.

Blending of the vaccine is performed by mixing the appropriate volumes of antigen and freeze-drying excipient under constant stirring. The vaccine bulk is immediately filled into the vials and the vials are subjected to the lyophilisation process. Lastly, the vials are closed with the stoppers and sealed with aluminium caps. The vaccine may be stored at 2 – 8 °C for 24 months. Samples for finished product control testing are taken. The information on the preparation of the vaccine bulk including filling and packaging is considered satisfactory.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Example certificates of analysis have been provided and all conform to the specifications in the respective Ph. Eur. monographs. A reference to the relevant Ph. Eur. monograph has been given. Where applicable, certificates of suitability and certificates of irradiation have been provided. The nature of the starting materials, controls and treatments applied guarantee sterility of the vaccine and absence of introduction of extraneous agents (EAs).

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

The following starting materials of biological origin are used at different stages of production of the vaccine: aMPV strain 1062, VERO cells, tryptose phosphate broth (TBP), microcarriers, trypsin and NZ amine. The information on the virus strain and the VERO cells is discussed in detail below. For all other starting materials of biological origin, satisfactory descriptions and CoAs were provided.

Avian metapneumovirus, strain 1062

The aMPV strain 1062 contained in the vaccine is derived from a field isolate from chickens with confirmed aMPV infection. The overall passage history from the original isolate to the passage constituting the master seed virus (MSV) as well as the MSV storage conditions are sufficiently described. The performed control tests on the aMPV MSV include virus titration, virus identification, bacterial and fungal sterility (Ph. Eur. 2.6.1), absence of mycoplasmas (Ph. Eur. 2.6.7) and testing for absence of those extraneous agents that could not be excluded by risk assessment. The corresponding CoA confirms that all results complied with the specifications. In addition to the testing results, a satisfactory risk assessment in accordance with Ph. Eur. 5.2.5 "Management of extraneous agents in immunological veterinary medicinal products (IVMPs)" was provided considering all extraneous agents applicable to the species of origin of the material (chicken), those of the target species (chicken) and possible contamination by any other material of animal origin used for MSV preparation.

The description of the aMPV strain 1062 working seed virus (WSV) prepared by passaging of the MSV on VERO cells and the storage conditions are also provided. The number of passages from the MSV for the vaccine manufacturing met the requirements of Ph. Eur. 0062. The WSV was found to be sterile according to Ph. Eur. 2.6.1 and the viral titre was determined. The corresponding CoA summarising the test results has been provided.

VERO cell line

The VERO cell line used to grow the aMPV antigen consists of fibroblast-like kidney cells from an African Green Monkey.

The history of the cell line in terms of origin, number of passages, media used, storage conditions and preparation are adequately described.

The corresponding CoA of the master seed cells (MSC) summarising the testing results is provided. The MSC were tested in accordance with Ph. Eur. 5.2.4 "cell cultures for the production of vaccines for veterinary use" for general microscopy, viability, karyotype, identity, endogenous retroviruses, absence of mycoplasmas, bacterial and fungal sterility and extraneous agents that could not be excluded by risk assessment. All methods were appropriately validated. A risk assessment in accordance with Ph. Eur. 5.2.5 considering all steps of passaging from the OC to the MSC and all extraneous agents applicable to the species of origin of the material (primate), those of the target species (chicken) and possible contamination by any other material of animal origin used for MSC preparation was provided.

The WSC were obtained by passaging of the MSC several times in cell cultures The number of passages, media used, storage conditions and preparation are adequately described.

The corresponding CoA, summarising the results of testing of the WSC for general microscopy, viability, bacterial and fungal sterility, absence of mycoplasmas and for absence of extraneous agents that could not be excluded by the risk assessment, is provided.

The working seed cells at the highest passage level have been tested in accordance with Ph. Eur. 5.2.4. All results complied with the specifications. The passage history (MSC to maximum passage used in production) of the VERO cells has been adequately described. The VERO cells are used in line with the requirements of Ph. Eur. 5.2.4.

Risk of transmitting animal spongiform encephalopathy (TSE) agents

All starting materials of animal origin including aMPV strain 1062 and the VERO cells were considered in the TSE risk assessment and comply with the current Ph. Eur. monograph 5.2.8 "Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products" and the TSE Note for Guidance (EMEA/410/01 rev.3). The overall conclusion that there is a negligible risk of remaining TSE infectivity in the vaccine is supported.

Starting materials of non-biological origin

The starting materials of non-biological origin are used as reagents or cell culture media at different stages of the manufacturing of the vaccine.

For use in production, CoA from the supplier(s) must show compliance with the starting material specifications. Specifications, together with representative CoA, are provided in the starting material monographs.

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

Several media and solutions used during vaccine production are in-house preparations. Detailed qualitative and quantitative composition, method of preparation and storage of such media and solutions prepared in-house are provided.

Control tests during the manufacturing process

The proposed control tests during the manufacturing process for the viral antigen and the freeze-drying excipient are considered adequate to support a consistent process. At different stages during the antigen manufacture, the viral titre is determined and a control test on sterility is performed. The viral titration follows a standard protocol and the defined acceptance criteria are considered appropriate. A protocol containing all necessary virus-specific details of the method including details on the controls and cells used, the cell culture media, the incubation conditions and the established validity criteria has been provided.

The freeze-drying excipient is tested for appearance, pH, density and bacterial and fungal sterility. The only test performed between the steps of vaccine blending to packaging of the finished product is the control of the filling volume. Sufficient information has been provided, including appropriate acceptance criteria for the tests performed on the freeze-drying excipient and for the control of the filling volume.

Results of the control tests carried out on three consecutive batches are provided and comply with the proposed specifications.

Control tests on the finished product

The general tests on the finished vaccine include a test on appearance and solubility. These tests are satisfactorily described and the specified acceptance criteria are appropriate.

The potency assay, used for identification and quantification of the aMPV antigen contained in the vaccine, is a virus titration. The protocol contains the vaccine-specific details of the methods. Details on the origin and the replacement strategies in place for all essential reagents have been satisfactorily described. The test has been appropriately validated considering the requirements of VICH GL1 and GL2 for validation of quantitative assays. The validated range is in accordance with the proposed final product specification of 1.8 to 5.4 $\log_{10}$ $CCID_{50}$/dose. The specificity of the assay considering other CPE-inducing viruses frequently handled at the manufacturing site has been demonstrated.

A validated finished product control test for sterility, according to the requirements of Ph. Eur. 2.6.1, was implemented and appropriately validated.

The test on the absence of mycoplasmas has been sufficiently described and validated in accordance with Ph. Eur. 2.6.7.

A brief risk assessment on the absence of extraneous agents in the final vaccine is provided. The risk assessment is considered to be in line with Ph. Eur. 5.2.5 because the main prerequisites for waiving of extraneous agents testing have been considered. The proposal to omit extraneous agents testing on the finished product is acceptable.

The control test for determination of the residual moisture of the lyophilised pellet of the vaccine is satisfactorily described and the proposed acceptance criteria are appropriately justified.

Batch-to-batch consistency

Data on three consecutive batches of the vaccine, each blended with a different batch of antigen, were provided. All batches were produced according to the described manufacturing process. The results complied with the proposed specifications for in-process control and finished product testing. Sufficient data on the intermediate steps of the antigen manufacture and on the batches of freeze-drying excipient used for blending of the presented vaccine batches are included in the batch

protocols. An appropriate batch protocol template has been submitted.

Stability

The intermediate storage of the concentrated antigen before blending as well as of the freeze-drying excipient were adequately supported by data.

A shelf life of 24 months during storage at 2 – 8 °C is proposed for the lyophilised vaccine. Real time stability data are presented for two batches over 27 months and for the third batch over 24 months. All batches were of industrial scale size and all available results complied with the proposed specifications. Updated stability data for the third batch should be provided until the complete data set is available.

In addition, pre-storage of the vaccine frozen at -20 °C ± 5 °C for 12 months before transfer to storage at 2 – 8 °C is proposed. Stability data complying with the proposed specifications are provided. In conclusion, pre-storage at -20 ± 5 °C for 12 months is considered acceptable.

An in-use stability of 2 hours, at room temperature (15 – 25 °C), after reconstitution according to the directions, is claimed for the vaccine. The data of two vaccine batches tested for viral titre and microbial contamination adequately support the proposed stability of the reconstituted vaccine.

The observed drop in titre over shelf life of the finished product or the reconstituted product has been considered in the release and end-of-shelf life specifications. In conclusion, the proposed shelf lives are considered acceptable.

Overall conclusions on quality

Respivac TRT contains the live attenuated strain 1062 of aMPV, subtype B as active substance and a complex freeze-drying excipient as stabiliser. The quantitative and qualitative composition of the vaccine presented as lyophilisate for suspension for oculonasal use (by spray administration) or use in drinking water is described.

The overall manufacturing process of the viral antigen, the freeze-drying excipient and the finished vaccine is described in sufficient detail. The viral strain is propagated on cells. The freeze-drying excipient is prepared by dissolution of all ingredients in water for injections. Vaccine blending is performed by mixing the antigen and the excipient. Details on the filling and lyophilisation process are provided.

Information on the starting materials has been provided and is acceptable. Sufficient details on the preparation and the passage histories of the virus and cell seeds are provided as well as for all starting materials of biological origin.

Appropriate in-process control tests are in place.

The finished product control tests are satisfactorily described and validated, if necessary.

Batch-to-batch consistency is considered to be sufficiently shown.

The proposed intermediate storage of the concentrated antigen before blending and the freeze-drying excipient is acceptable. The proposed shelf life of the vaccine for 24 months at 2 – 8 °C with a potential pre-storage at -20 °C for 12 months is adequately supported by data. Nevertheless, the pending results of the stability study should be submitted. The in-use stability is satisfactorily supported by data.

In general, the data on quality, manufacture and control of Respivac TRT can be considered acceptable.

Recommendations

The applicant is recommended to provide the following data post-opinion:

- The completed real-time stability study of Respivac TRT after storage for 27 months at 2 – 8 °C.

Part 3 – Safety documentation (safety and residues tests)

General requirements

The active substance of Respivac TRT is the live attenuated avian metapneumovirus (aMPV) strain 1062 (subtype B). The proposed virus titre per dose is $10^{1.8}$–$10^{5.4}$ $CCID_{50}$. Excipients included in this vaccine are dextran, sucrose, gelatine, NZ amine, sorbitol, potassium dihydrogen phosphate and dipotassium phosphate.

A full safety file in accordance with Article 8(1)(b) of Regulation (EU) 2019/6 has been provided. Studies to determine the safety of the vaccine were performed in accordance with section IIIb of Annex II to Regulation (EU) 2019/6, Ph. Eur. monograph 0062 on "vaccines for veterinary use", Ph. Eur. chapter 5.2.6 on the "evaluation of safety of veterinary vaccines and immunosera", Ph. Eur. monograph 2461 "Turkey infectious rhinotracheitis vaccine (live)", which was adapted to the target species chickens, and VICH GL41 "Target animal safety: examination of live veterinary vaccines in target animals for absence of reversion to virulence".

The vaccine is intended for the active immunisation of chickens via the oculonasal route by spraying from the 1st day of life or for use in drinking water from the 7th day of life to reduce the respiratory signs caused by virulent strains of aMPV. For a prolonged immunity, a revaccination every 9 weeks and also throughout the laying period is recommended.

The vaccine consists of a lyophilisate, which is reconstituted in clean, fresh, antiseptic- and disinfectant-free water. It is presented in cardboard boxes with 1 or 10 vials, with the lyophilisate containing 1,000, 2,000, 5,000 or 10,000 doses.

Safety documentation

Nine safety studies were conducted to investigate the safety of the product. These include five pre-clinical studies and four clinical trials. Out of the five pre-clinical studies, two were investigating the safety of the administration of a 10-fold overdose and repeated dose and the safety for the reproductive performance; three studies, applicable to live vaccines, were conducted to investigate the dissemination of a single dose of the vaccine strain, the spread from vaccinated animals to non-vaccinated contact animals (target species and non-target species) and reversion to virulence.

The vaccine was administered by the oculonasal route by spray administration, as recommended. The drinking water route was only investigated during two of the field trials. In the spread, dissemination and reversion to virulence studies eye-drop application was chosen instead of spray application to ensure that the complete dose was administered to the birds. This is considered a worst-case scenario for the demonstration of safety and is therefore considered an acceptable approach.

All pre-clinical studies were reported to be GLP-compliant. They were carried out in chickens of the minimum age recommended for vaccination, using a pilot batch of industrial scale or the MSV. The four

clinical studies were GCP-compliant, multicentred, randomised and double-blinded and were provided to assess both the safety and efficacy of Respivac TRT under field conditions. Two of these four studies were carried out in broiler chickens and the other two in broiler breeders using the oculonasal route via spray and drinking water administration. A pilot batch of industrial scale was used in the clinical trials.

Study title	*Potency of batch used*
10x overdose and repeated single dose	10x Maximum dose or maximum dose
Safety of reproductive tract	Maximum dose
Spread (target species + non-target species)	Maximum dose
Dissemination	Maximum dose
Increase in virulence	Maximum dose
Field study in future hens	Standard dose
Field study in broilers	Standard dose
Field study in future hens	Standard dose
Field study in broilers	Standard dose

Pre-clinical studies

For all pre-clinical studies SPF chickens were used. SPF certificates to confirm their status are provided. The applicant has established relevant scoring systems and humane end-point criteria to maximise animal welfare during the studies. Relevant study protocols are provided, for pre-clinical studies and for clinical trials.

Safety of the administration of one dose

No single dose study is provided with the justification that a single dose safety test can be omitted when a 10x overdose study is provided. Indeed, the overdose study supported the safety of a single dose, and, thus, no specific one-dose safety study was performed. This is acceptable and in line with Annex II to Regulation (EU) 2019/6 as amended.

Safety of one administration of an overdose

One pivotal overdose study combined with the evaluation of a repeated maximum single dose was provided. A 10-fold maximum overdose containing $10^{6.4}$ $CCID_{50}$/dose was administered by spray to 1-day-old SPF chickens. At 14 days of age, the same chickens were re-vaccinated by spray with a maximum single dose of $10^{5.4}$ $CCID_{50}$.

The vaccinated chickens were observed for clinical signs and mortality for 14 days after each vaccination. At the end of the study, all chickens were sacrificed for necropsies with special focus on the respiratory tract. No clinical signs or deaths were noted. No macroscopic lesions were found, histopathologic evaluations were not performed.

The vaccine virus is considered safe for chickens when given at a 10x maximum dose and a repeated maximum single dose via spray at an interval of 14 days. This short interval presents a worst-case scenario considering that a revaccination with Respivac TRT at an interval of 9 weeks is proposed.

The second administration route via drinking water at a minimum age of 7 days of life was not assessed in this study. This approach is regarded as acceptable because spraying is considered the

more critical route resulting potentially in adverse reactions. This is in line with Ph. Eur. monograph 2461; the droplet size used for spraying is indicated in the product information. Furthermore, two field trials are provided in which administration route via drinking water was evaluated in broilers and also in future broiler breeders.

In conclusion, the information provided is considered satisfactory.

Safety of the repeated administration of one dose

The safety of a repeated administration of one dose was evaluated together with the safety of an overdose.

Examination of reproductive performance

Respivac TRT is primarily intended for young chickens. However, the option to revaccinate chickens every 9 weeks and also during lay, to prolong their immunity, was also considered. Therefore, the influence of the vaccination with Respivac TRT on the laying performance was assessed.

A group of fifteen (+ 10 replacements) 26-week-old female SPF chickens was monitored for general health and for their laying performance 4 weeks before vaccination and 4 weeks after the vaccination via spray at an age of 30 weeks. Egg quantity and quality (albumen, yolk and egg shells) were evaluated as well as the possible vaccine virus occurrence in the eggs. At the end of the study, necropsies were performed with special focus on the reproductive tract.

No clinical signs or mortality related to the vaccination were observed. No differences in laying performance were found before or after vaccination and no relevant alterations of egg quality were detected. No virus was detected in any egg. In the pathological examinations no relevant lesions were found.

The hen group examined was relatively small. However, the applicant provided an acceptable rationale on why this number of chickens was chosen. The chickens were vaccinated only once, whereas the proposed vaccination scheme includes revaccinations every 9 weeks during lay. It is acknowledged that two field trials are provided in which future broiler breeders were vaccinated once and followed up until 9 weeks of age. No clinical signs or increased mortality were noted in these trials. Furthermore, during the dissemination study no evidence of virus could be detected in oviducts. Data are presented for the necropsies at the end of the combined overdose and repeated dose study to prove that no alterations of the reproductive tract were detected.

Examination of immunological functions

No further studies were conducted to investigate the effects of the product on immunological functions, but no adverse effects were observed in any of the safety or efficacy studies. It is therefore unlikely that this vaccine will have an adverse effect on immunological functions due to the nature of the product (live vaccine virus without any known immunosuppressive effects).

Special requirements for live vaccines

Spread of the vaccine strain

Spread from vaccinated SPF chickens to naïve SPF chickens and to seronegative turkeys as the most

susceptible non-target species (natural host of aMPV) was investigated. For this aim, the MSV was used at a single maximum dose of $10^{5.7}$ $CCID_{50}$ and applied via eye drop at the first day of life. The naïve or seronegative birds were mingled with the vaccinated chickens for a duration of three weeks. Blood samples and oropharyngeal swabs were collected for serology and vaccine virus detection and quantification. General health observation was carried out daily.

Serology data was not relevant, as anticipated by the applicant. No clinical signs or deaths related to the vaccination were noted throughout the observation period. Detection and quantification of aMPV in oropharyngeal swabs by RT-qPCR revealed that the virus was secreted by vaccinated chickens at least until day 21 (last day of testing). The vaccine virus could also be detected in swabs from in-contact animals but with lower virus burden and for a shorter period compared to the swabs from vaccinates, indicating a limited capacity of the vaccine virus to spread. However, it can be concluded that the vaccine virus spreads from vaccinated chickens to naïve chickens and also to seronegative turkeys. The SPC was adapted accordingly.

Dissemination in the vaccinated animal

Dissemination of the vaccine strain in vaccinated animals was investigated in one study using the MSV at a single maximum dose of $10^{5.7}$ $CCID_{50}$ applied via eye drop at the first day of life. On days 3, 5, 7, 10, 14 and 21, respectively, six chickens were sacrificed and the following samples were taken to evaluate the dissemination of the vaccine virus: oropharyngeal and cloacal swabs, nasal and periorbital swabs, samples of trachea, lung, Harderian gland and oviduct. Blood was collected from the last subgroup of chickens, which were observed for the longest period until 21 days post vaccination. Additionally, the chickens were observed for general health, clinical signs and mortality.

Serology data was not relevant. No clinical signs or deaths were reported during the study. Vaccine virus was detected in oropharyngeal swabs until day 21 (last day of testing), but the virus was only quantifiable until day 14. In cloacal swabs no virus was detected at any time. Samples of lung, Harderian gland and oviduct were also negative at each point in time. Nasal swabs were positive for aMPV until day 10 and again on day 21, but the virus was quantifiable only until day 10. Periorbital swabs were positive for aMPV until day 10 and the virus was quantifiable until day 7. In the trachea samples virus was found on days 3, 5 and 10, but was only quantifiable on day 3. In summary, it was demonstrated that the vaccine virus disseminates to the upper respiratory tract of chickens and is excreted via respiratory secretions at least for 21 days.

Increase in virulence of attenuated vaccines

Reversion to or increase in virulence was evaluated, as required for live vaccines. The MSV was applied with a single maximum dose of $10^{5.7}$ $CCID_{50}$ via eye-drop to a first batch of five SPF chickens. Besides clinical observations, oropharyngeal swabs were collected and pooled on day 5 post vaccination and discharged in cell culture media to obtain a virus suspension for the next virus passage. AMPV was detected with $10^{9.25}$ $DICC_{50}$/ml in the first passage. In this study, 0.1 ml of this virus suspension (= MSV+1) was applied to the next batch of SPF chickens according to Ph. Eur. monograph 2461. Since the virus was not recovered after the second passage, this passage was repeated with ten chickens. Again, no vaccine virus was detected; therefore, no further passages were required according to Ph. Eur. monograph 2461 and the test was stopped because the vaccine virus complied with the test. The method is adequate to detect aMPV and therefore no reversion to or increase in virulence was detectable. No clinical signs or deaths were noted in this study.

It was noted that different batches of SPF chickens originating from the same eggs supplier but hatched at two different sites were used. The applicant confirmed that the same conditions are present

at both sites.

Biological properties of the vaccine strain

No specific studies have been conducted to determine the intrinsic biological properties of the vaccine strain. In the studies conducted, the vaccine strain did not cause clinical signs, lesions or deaths to vaccinates.

On the basis of the data presented, the safety profile of the strain can be considered acceptable.

Recombination or genomic reassortment of the strains

No specific study evaluating a recombination or a genomic reassortment of the vaccine strain with other aMPVs was performed.

The risk of recombination or genomic reassortment of the vaccine strain is considered negligible by the applicant for the following reasons:

- vaccination programs for chickens include only vaccines against the most prevalent subtype. Therefore, no other subtypes of aMPV vaccines will be present on a farm.
- the occurrence thereof is very improbable as two different viruses have to infect the same cell at the same time. Based on literature data, all negative-sense RNA viruses are known for low rates or absence of recombination.
- in the reversion to virulence study only a limited ability of passaging in chickens was observed.

It can be concluded that the event of recombination or genomic reassortment is very unlikely. This assessment was made in compliance with the respective legal requirements. This approach and conclusions are considered acceptable.

User safety

The applicant has presented a user safety risk assessment, which has been conducted in accordance with the CVMP guideline on "User safety for immunological veterinary medicinal products" (EMEA/CVMP/IWP/54533/2006).

In the frame of this assessment, the main potential routes of accidental contact with the product have been considered, and it was concluded that dermal and ocular exposure are the most likely routes of user exposure. The risk of inhalation during spraying was also assessed. However, the vaccine virus strain 1062 is not pathogenic to 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 applicant included some adequate advice/warnings for the user in section 3.5 of the SPC.

It can be concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

MRLs

The active substance in Respivac TRT is of biological origin, intended to produce active immunity, and is therefore not within the scope of Regulation (EC) No 470/2009.

The excipients listed in section 2 of the SPC are either allowed substances for which no MRLs are required according to Table 1 of the Annex to Commission Regulation (EU) No 37/2010 or are considered not to fall within the scope of Regulation (EC) No 470/2009 when used as in this product.

During the production process, antimicrobials are used. The applicant has provided a calculation of residues likely to be present in the finished product. Based on these results, it can be concluded that the amounts remaining in the finished product will be below the established maximal residues limits and with no pharmaceutical activity.

Withdrawal period

The withdrawal period is set at zero days.

Interactions

The applicant has not provided data investigating interactions of the vaccine with any other veterinary medicinal product and, therefore, proposes to include a statement in Section 3.8 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."* This approach is accepted.

Clinical studies

Four pivotal GCP compliant, randomised, double-blinded, positive or negative controlled studies of parallel group design were conducted to evaluate the safety and efficacy of Respivac TRT in broiler chickens or future broiler breeders at a standard dose. The studies were performed in France and in Belgium in commercial farms.

In the farms, the studies were performed in two similar houses and, in one case, in two different farms, each with two similar houses. The studies in France were performed in future broiler breeders using a comparator vaccine in a positive control group. The trials in Belgium were performed in commercial broiler chickens using non-treated negative control groups (untreated drinking water was provided). In all studies, a single standard dose of Respivac TRT was used. No evidence of a field infection with aMPV was detected; therefore, no efficacy parameters were evaluated.

In the field trials with future broiler breeders, in summary, 26,350 chickens and 22,348 chickens, respectively, were vaccinated either with the test product or with a comparator vaccine. In the study intended to assess drinking water the chickens were vaccinated at 7 days of age and in the study to assess spray administration, at 1 day of age. In both trials, the chickens were followed up until day 63 post vaccination.

In the studies with broiler chickens, 71,212 chickens and 189,700 chickens were included, respectively. In the field trials in broilers, in one study the vaccine was applied at 7 days of age via drinking water and in the other study at 1 day of age via spray. The broiler chickens of both trials were followed up

until slaughter at 41 days of age.

In all clinical studies, the MDA level before vaccination was determined. In all cases, MDA levels were high on day 0 and decreased until day 7 (serology on day 7 was only performed when the chicks were vaccinated at 7 days of age). Development of body weight was measured in 100 animals/group and clinical signs and mortality were recorded. The body weight development was similar in all groups in all trials, with no differences between groups at the end of the study. The same applies to observations on clinical signs and mortalities. Mortalities were always in the usual range of the respective farm and not clinically relevant. The broiler flocks were treated several times with antibiotics because of outbreaks of colibacillosis and enteritis. However, this is not unusual for this type of chickens.

It is noted that the chickens were only followed up until 63 days of life (not until lay) and no necropsies with special focus on the reproductive tract of a small group of hens were performed in future broiler breeders, which would have been beneficial for the evaluation of the safety of the vaccination for the reproductive tract in the field. The applicant should consider for future studies to prolong the study period and to evaluate the reproductive tract of some hens. Study protocols for all studies are provided.

In conclusion, all these data support the safety of Respivac TRT when administered by the recommended routes under commercial conditions.

Environmental risk assessment

The environmental risk assessment showed that the overall risk of the vaccine to the target and non-target species, the user and the environment is effectively zero. The "Note for guidance on environmental risk assessment for immunological veterinary medicinal products" (EMEA/CVMP/074/95) was considered.

Considerations for the environmental risk assessment

The live attenuated aMPV strain 1062 is not considered to be pathogenic for humans. It is not recognised as a zoonotic virus strain or pathogenic to other species besides avian species. There was no increase in virulence noted, as the strain was not detectable after two animal passages. Spread of the vaccine strain was demonstrated from vaccinated to naïve SPF chickens as well as to seronegative turkeys without any clinical consequences. The vaccine virus was excreted through oropharyngeal secretions of vaccinated animals for at least 21 days.

Reassortment or recombination of vaccine strain 1062 with other aMPV vaccine strains is very unlikely. In the safety studies, a high safety profile was demonstrated for strain 1062. Handling, hygiene and disinfection routines on farms will avoid the persistence of the virus in the environment.

All other components of the vaccine are not considered to pose any risk to the environment.

Based on the data provided, the ERA can stop at Phase I. Respivac TRT is not expected to pose a risk to the environment when used according to the SPC.

Overall conclusions on the safety documentation

Nine safety studies (five pre-clinical studies and four clinical trials) were conducted to investigate the safety of the product.

One pivotal pre-clinical study is provided to investigate the safety of a 10-fold overdose containing

$10^{6.4}$ $CCID_{50}$/dose and also the repeated administration of one maximum dose of $10^{5.4}$ $CCID_{50}$ to chickens of the minimum recommended age of 1-day-old at an interval of 14 days via the oculonasal route by spray. The drinking water route to 7-day-old chickens was not evaluated because spray administration is considered the more critical route resulting potentially in adverse reactions. These findings were supported by the data generated in four field trials performed in European Union countries, in commercial broiler chickens or future broiler breeders vaccinated by spray or via the drinking water route.
The short interval of 14 days between vaccinations represents a worst-case scenario considering that a revaccination with Respivac TRT at an interval of 9 weeks is proposed.

Reproduction safety was also investigated. The product was found to be safe when used in laying hens.

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

As this is a live vaccine, the applicant also conducted two studies to establish the potential for spread and dissemination of the vaccine strain. Excretion via the respiratory tract was found at least for 21 days. This period has been reflected in the SPC. Spread from vaccinated to unvaccinated chickens and turkeys did not result in any clinical signs. The vaccine strain disseminated to the upper respiratory tract of vaccinated chickens.

Reversion to virulence was also investigated. The results showed that the potential risk is very low. The risk of recombination and the genomic re-assortment of the strain and also the biological properties of the vaccine strain were described adequately and found to be acceptable.

On the basis of the results, it was concluded that the safety for the target animals is acceptable when the product is administered according to the recommended schedule and via the recommended route.

A satisfactory user safety assessment has been presented. The potential health risk of the product to all users is considered low and acceptable when used in accordance with the SPC, as the virus is not pathogenic for humans.

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk to the environment when used according to the SPC.

In summary the use of Respivac TRT in chickens when used according to the product information is considered safe in the target species.

Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)

General requirements

Respivac TRT is a live attenuated vaccine against infection with avian metapneumovirus (aMPV) in chickens. The vaccine consists of a live attenuated aMPV, strain 1062. The vaccine is presented as lyophilisate for oculonasal suspension/use in drinking water in type I glass vials, to be reconstituted before use in clean, fresh, antiseptic- and disinfectant-free water.

The vaccine is intended to reduce the respiratory signs caused by virulent avian metapneumovirus, when administered to chickens

- by oculonasal route (spray administration) from 1 day of age or
- in drinking water from 7 days of age.

The vaccination scheme consists of one single administration. For prolonged immunity, chickens could be vaccinated every 9 weeks (according to the local epidemiological situation). The minimum dose is $10^{1.8}$ $CCID_{50}$/dose* (*50% cell culture infective dose).

Immunity is intended to be established from 3 weeks post vaccination.

A single vaccination is sufficient to provide protection for 9 weeks post vaccination.

Efficacy was demonstrated in compliance with Regulation (EU) 2019/6 as amended, Ph. Eur. chapter 5.2.7: Evaluation of efficacy of veterinary vaccines and immunosera and Ph. Eur. monographs 2461: Turkey Infectious Rhinotracheitis Vaccine (Live) and 0442: Avian Infectious Bronchitis Vaccine (live).

Challenge model

The aMPV challenge strain 1076 used in the laboratory efficacy studies was originally isolated in an Italian farm, from hens affected by an outbreak of respiratory disease in 2002. The strain was confirmed to be a subtype B strain. It is considered heterologous to the vaccine strain isolated in 1988 and relevant to the current epidemiological situation in Europe according to the classification based on the sequence of the G protein performed by Cecchinato *et al.* 2010, where two groups of field strains have been established depending on the year of detection (strains pre-1994 and strains post-2000). The sequence of the G protein, on which the classification is based, has been provided and commented on for both the vaccine strain 1062 and the challenge strain 1076, which confirmed the differences between the strains. The preparation of the in-house challenge stock from the purchased original IT/Ck/34a/02 was described. The certificate of analysis (CoA) has been presented.

The challenge model was designed according to the requirements of the Ph. Eur. chapter 5.2.7, and, as far as possible being for a different species, according to the Ph. Eur. monograph 2461. The challenge was administered 21 days after vaccination by oculonasal route, mimicking the natural conditions for infection, at a dose of $10^{5.0}$ ciliostatic dose 50 (CD_{50})/0.1 ml to SPF and commercial chickens. Chickens were observed daily for at least 10 days after challenge and clinical signs were monitored individually. In case of death, birds were examined and lesions of the respiratory tract were checked.

Ph. Eur. monograph 2461 applies to vaccines intended for administration to turkeys, while Respivac TRT is intended to be administered to chickens. In the field, aMPV can cause clinical signs and lesions in chickens, but in the laboratory, clinical signs and lesions were considered non-valuable parameters to determine the vaccine effect under experimental conditions.

Since aMPV causes loss of ciliary activity that results in respiratory signs as well, ciliary activity was chosen as primary efficacy parameter to determine whether chicks show respiratory signs. Assessment was done according to the Ph. Eur. Monograph 0442 (specific for avian infectious bronchitis - IB - vaccines, live), section 2-3-3-1. Given the differences in viral pathogenicity between aMPV and avian infectious bronchitis virus, some requirements of the IB monograph were adapted for aMPV: the day of euthanasia of the chicks for the ciliary activity evaluation (10 - 11 days for aMPV), the criteria to define a vaccine as valid (the proportion of chicks with respiratory signs - based on the tracheal ciliary activity assessment - is significantly lower in vaccinated chicks than in mock-vaccinated) and the validity criteria for the challenge in the unvaccinated animals.

One challenge model development study demonstrates that strain 1076 administered by eye and nostril drop is suitable to reproduce respiratory signs in chickens and, hence, suitable to assess the efficacy of aMPV vaccines. The incidence of ciliary effects caused by aMPV in unvaccinated chickens was

estimated as *p0* = 0.70 (7/10 affected chicks). The final study report of the challenge model development study has been provided.

Efficacy parameters and tests

The efficacy parameters investigated in the efficacy studies are:

Primary parameter:

- Respiratory signs after challenge based on the tracheal ciliary activity assessment according to Ph. Eur. 0442, sufficiently described in a SOP.

Secondary parameters:

- Clinical signs, daily post challenge (i.e. general clinical signs, respiratory clinical signs, nervous signs, other signs, dead/euthanised).
- Macroscopic lesions, paying special attention to the upper respiratory tract.
- Body weight gain post challenge.

The serological status of the birds was checked before vaccinations and before challenge by ELISA. The method and its validation have been provided.

The parameters chosen are in line with the requirements of Ph. Eur. chapter 5.2.7 as well as monographs 2461 and 0442 adapted to aMPV in chickens as described above and, therefore, are considered appropriate for evaluating the efficacy of the product.

Efficacy documentation

Twelve studies were conducted to investigate the efficacy of the product (eight pre-clinical studies and four clinical trials). Laboratory studies were well documented and carried out in short-lived (broilers) and long-lived (future layers) SPF chickens as well as in MDA-positive commercial broiler birds of the minimum age recommended for vaccination.

The batches used were representative pilot batches of the production method described in Part 2.B of the dossier, at the most attenuated passage level that will be present in the vaccine, with a dose not higher than the minimum titre ($10^{1.8}$ $CCID_{50}$). The passage level of the batches used was MSV+5.

The laboratory efficacy tests were conducted according to OECD Principles of Good Laboratory Practices (99/11/CE, 1997). The combined field safety and efficacy trials adhered to the requirements of Good Clinical Practice (GCP).

Overview of the laboratory efficacy studies:

Pre-clinical studies

Study reference	Study title	Admini-stration route/age	Titre adm. ($CCID_{50}$/ds)
Onset of immunity (with or without MDA)			
	Study on the influence of maternally derived antibodies (MDA) and onset of immunity of Respivac TRT vaccine by oculo-nasal route against avian metapneumovirus (aMPV) in **short-lived** chickens.	Spray/ 1 day	$10^{1.8}$
	Study on the influence of maternally derived antibodies (MDA) and onset of immunity of Respivac TRT vaccine administered by drinking water against avian metapneumovirus (aMPV) in **short-lived** chickens.	Drinking water/ 7 days	$10^{1.8}$
	Study of the onset of immunity of Respivac TRT vaccine administered by oculo-nasal route against avian metapneumovirus (aMPV) in **long-lived** chickens.	Spray/ 1 day	$10^{1.8}$
	Study of the onset of immunity of Respivac TRT vaccine administered by drinking water against avian metapneumovirus (aMPV) in **long-lived** chickens.	Drinking water/ 7 days	$10^{1.78}$
Duration of immunity			
	Study of the duration of immunity of Respivac TRT vaccine administered by oculo-nasal route against avian metapneumovirus (aMPV) in **short-lived** chickens.	Spray/ 1 day	$10^{1.8}$
	Study of the duration of immunity of Respivac TRT vaccine administered by drinking water against avian metapneumovirus (aMPV) in **short-lived** chickens.	Drinking water/ 7 days	$10^{1.8}$
	Study of the duration of immunity of Respivac TRT vaccine by oculonasal route against avian metapneumovirus (aMPV) in **long-lived** chickens.	Spray/ 1 day	$10^{1.8}$
	Study of the duration of immunity of Respivac TRT vaccine administered by drinking water against avian metapneumovirus (aMPV) in **long-lived** chickens.	Drinking water/ 7 days	$10^{1.68}$

Dose determination

No explicit study on the determination of the vaccine dose has been performed. However, the proposed minimum efficacious dose ($10^{1.8}$ $CCID_{50}$) has been evaluated in the efficacy laboratory studies and it is considered supported.

Onset of immunity

Four studies designed and validated according to the requirements of Ph. Eur. chapter 5.2.7, Ph. Eur. monograph 2461, when possible, and Ph. Eur. Monograph 0442 regarding the main efficacy parameters were performed to determine the efficacy and onset of immunity for aMPV in short-lived (broilers) and long-lived (future layers) SPF chickens, two studies including birds vaccinated via oculonasal (spray) route and two using birds vaccinated via drinking water.

In summary, the chickens in these studies were vaccinated via spray (1 day old) or via drinking water (7 days old) with a dose of minimum titre or below ($10^{1.78}$ - $10^{1.8}$ $CCID_{50}$). Challenge was performed 21 days post vaccination, as required by Ph. Eur. monograph 2461, for both routes of vaccination, with $10^{5.0}$ CD_{50}/dose of the virulent aMPV challenge strain 1076, via oculonasal route. The claimed onset of immunity (3 weeks) corresponds to the time of challenge in the above-mentioned Ph. Eur. for the immunogenicity test. The chickens were observed for 14 days after challenge for mortality and clinical signs. Post-mortem examination was performed on all dead or euthanised birds and also on all remaining birds after the observation period. At days 10 and 11 post challenge, 8 or 12 chickens per group were euthanised to evaluate respiratory signs based on the tracheal ciliary activity. Body weight was measured and the serological status of the birds was checked at day 0, before challenge and at day 35.

According to the challenge model study, the expected proportion of unvaccinated birds showing typical signs of respiratory disease (based on the tracheal ciliary activity assessment) following challenge with the virulent aMPV is *p0*=0.07. The vaccine complies with the test if statistically significant differences in the proportion of chicks with respiratory signs (based on the tracheal ciliary activity assessment) are found between vaccinated and control groups.

The following studies were performed to assess onset of immunity (two studies included two additional groups of chicks with MDA, which are discussed later when assessing the influence of MDAs on the vaccine):

In the study performed by spray administration at one day of age in short-lived chickens, two groups (A and C) of 33 1-day-old short-lived SPF chickens and two groups (B and D) of 33 1-day-old short-lived commercial chickens with MDA were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to groups A and B by the oculonasal route. Groups C and D were mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. Chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 100% of the non-vaccinated/challenged control groups (C and D) showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 75% in SPF (group A) and 87.5% in MDA+ (group B) chickens (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups.
Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and vaccinated SPF birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study performed by drinking water administration at 7 days of age in short-lived chickens, two groups (A and C) of 33 1-day-old short-lived SPF chickens and two groups (B and D) of 33 1-day-old short-lived commercial chickens with MDA were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to groups A and B by drinking water. Groups C and D were mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 87.5 and 100% of the non-vaccinated/challenged control groups (C and D, respectively) showed typical signs of respiratory disease (based on the tracheal ciliary

activity assessment). The level of percentage of protection after challenge was 100% in the SPF (group A) and in the MDA+ (group B) chickens (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups.

Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and corresponding controls after the challenge. All control and vaccinated SPF birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study performed by spray administration at one day of age in long-lived chickens, two groups (A and B) of 38 1-day-old long-lived SPF chickens were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to group A by the oculonasal route. Groups B was mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 100% of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 100% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups.

Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and vaccinated SPF birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study by drinking water administration at 7 days of age in long-lived chickens, two groups (A and B) of 38 1-day-old long-lived SPF chickens were used. A vaccine dose of $10^{1.78}$ $CCID_{50}$ was administered to group A by drinking water. Groups B was mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 91.67% of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 100% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and vaccinated SPF birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds but one of the vaccinated group A showed a high titre of aMPV-specific antibodies.

It was concluded that vaccination with a dose of the minimum content (or below) recommended in the SPC was efficacious and met the efficacy requirements from 3 weeks after vaccination when administered oculonasally by spray from one day of age or by drinking water from 7 days of age to short-lived and long-lived chickens.

As there were no statistically significant differences between vaccinated birds and the corresponding controls regarding clinical signs in the presented studies, the claim to reduce the respiratory signs caused by virulent avian metapneumovirus could only be supported regarding the detrimental effect on the ciliary activity resulting from the infection by virulent avian metapneumovirus, which may be manifested in respiratory clinical signs. Section 3.2 of the SPC has been amended accordingly.

Duration of immunity

Four studies designed and validated according to the requirements of Ph. Eur. 5.2.7, the Ph. Eur.

monograph 2461, when possible, and Ph. Eur. Monograph 0442 regarding the main efficacy parameters were performed to determine the duration of immunity for aMPV in short-lived (broilers) and long-lived (future layers) SPF chickens. Two studies were including birds vaccinated via oculonasal (spray) route and two other studies were including birds vaccinated via drinking water.

In summary, the chickens in these studies were vaccinated via spray (1 day old) or via drinking water (7 days old) with a dose of the minimum titre or below ($10^{1.68}$ - $10^{1.8}$ $CCID_{50}$). Challenge was performed 9 weeks post vaccination for both routes of vaccination with $10^{5.0}$ CD_{50}/dose of the virulent aMPV challenge strain 1076 via oculonasal route.

The chickens were observed for 13/14 days after challenge for mortality and clinical signs. Post-mortem examination was performed on all dead or euthanised birds and on all remaining birds after the observation period. At days 10 and 11 post challenge, 8 or 12 chickens per group were euthanised to evaluate respiratory signs based on the tracheal ciliary activity. Body weight was measured at days 0, 20, 42, before challenge and at day 76/77. The serological status of the birds was checked at day 0, before challenge and at day 76/77.

According to the challenge model study, the expected proportion of unvaccinated birds showing typical signs of respiratory disease (based on the tracheal ciliary activity assessment) following challenge with the virulent aMPV is $p0$=0.07. The vaccine complies with the test if statistically significant differences in the proportion of chicks with respiratory signs (based on the tracheal ciliary activity assessment) are found between vaccinated and control groups.

<u>The following studies were performed to assess duration of immunity:</u>

In the study performed by spray administration at one day of age in short-lived chickens, two groups (A and B) of 29 1-day-old short-lived SPF chickens were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to group A by the oculonasal route. Group B was mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 63 days (9 weeks) post vaccination. The challenge was valid as 100% of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 75% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and all but one vaccinated birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study performed by drinking water administration at 7 days of age in short-lived chickens, two groups (A and B) of 33 7-day-old short-lived SPF chickens were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to group A by drinking water. Group B was mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 63 days (9 weeks) post vaccination. The challenge was valid as 100% of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 100% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and all but one vaccinated bird remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study performed by spray administration at one day of age in long-lived chickens, two groups (A and B) of 38 1-day-old long-lived SPF chickens were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to group A by the oculonasal route. Group B was mock-vaccinated with clean, fresh, antiseptic- and disinfectant-free water. The chickens were challenged with virulent aMPV at 63 days (9 weeks) post vaccination. The challenge was valid as 83.3% of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 100% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and all but two vaccinated birds remained seronegative up to the time of challenge. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In the study performed by drinking water administration at 7 days of age in long-lived chickens, two groups (A and B) of 38 7-day-old long-lived SPF chickens were used. A vaccine dose of $10^{1.68}$ $CCID_{50}$ was administered to group A by drinking water. Group B was mock-vaccinated with clean, fresh, antiseptic and disinfectant-free water. The chickens were challenged with virulent aMPV at 63 days (9 weeks) post vaccination. Sixty-six point seven percent (66.7%) of the non-vaccinated/challenged control group B showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The challenge is considered to be valid since the probability of observing 8 out of 12 animals with ciliary activity effects (66.67%) when the expected proportion of animals with such signs is p0 = 0.70 is a highly likely outcome within all potential combinations. The level of percentage of protection after challenge was 100% in chickens of group A (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups.

Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge. All control and vaccinated birds remained seronegative up to the time of challenge. Thirteen days after challenge, all birds showed a high titre of aMPV-specific antibodies.

In these four challenge studies 9 weeks post vaccination, which is the claimed duration of immunity, significant difference in protection was demonstrated between vaccinated groups and controls, supporting sufficiently the proposed duration of immunity for both application routes in short-lived and long-lived chickens.

In conclusion, the claimed duration of immunity of 9 weeks post vaccination is adequately supported in the studies presented.

The presented data from four pre-clinical studies under the worst-case scenario (SPF chickens of the minimum recommended ages) for both administration routes and for the different types of birds (short-lived (meat type) and long lived (egg type)) also support the proposed possible revaccination every 9 weeks for a prolonged immunity. The re-vaccination dosage (one single dose) is the same as the initial vaccination dosage (one single dose), already assessed under the worst-case scenario (most sensitive animals); therefore, the expected duration of protection is considered at least the same. From the safety side, revaccination with Respivac TRT has been demonstrated in two studies: the repeated administration of one dose in the most sensitive categories and as the administration of the vaccine in laying hens. Thus, the safety of the administration of Respivac TRT during lay has been satisfactorily demonstrated.

As there were no statistically significant differences between vaccinated birds and corresponding controls regarding clinical signs in the presented studies, the claim to reduce the respiratory signs

caused by virulent avian metapneumovirus could only be supported regarding the detrimental effect on the ciliary activity resulting from the infection by virulent avian metapneumovirus, which may be manifested in respiratory clinical signs. Section 3.2 of the SPC has been amended accordingly.

Duration of immunity was not investigated in MDA-positive birds, which is considered acceptable as it was demonstrated that MDAs do not interfere with vaccine efficacy.

Maternally derived antibodies (MDA)

The studies were performed following the EMA reflection paper EMA/CVMP/IWP/439467/2007:

- Three groups of birds (MDA+ non-vaccinated, MDA- vaccinated and MDA+ vaccinated at the minimal age recommended for use) plus a fourth group of MDA- non-vaccinated birds were included in the studies.
- Challenges were performed 21 days post vaccination when the MDA levels had decreased to sufficiently low levels.
- It was shown that the efficacy of the vaccine in birds vaccinated in the presence of MDAs is, notwithstanding normal biological variation, similar to that obtained in birds of the same age but vaccinated in the absence of MDAs.

Two studies designed and validated according to the requirements in the Ph. Eur. chapter 5.2.7, as far as possible according to the Ph. Eur. monograph 2461 and the Ph. Eur. Monograph 0442 regarding the main efficacy parameters were performed to determine the efficacy for aMPV in short-lived (broiler) chickens with maternal antibodies, one including birds vaccinated via oculonasal (spray) route and one using birds vaccinated via drinking water.

In summary, chickens with and without maternal antibodies were vaccinated via spray (1 day old) or via drinking water (7 days old) with a dose of the minimum titre ($10^{1.8}$ $CCID_{50}$). Challenge was performed 21 days post vaccination for both routes of vaccination with $10^{5.0}$ CD_{50}/dose of the virulent aMPV challenge strain 1076 via oculonasal route. The claimed onset of immunity (3 weeks) corresponds to the time of challenge mentioned in the Ph. Eur. for the immunogenicity test. The aMPV serology was performed, for all treatment groups, on day 0, before challenge and on day 35 to determine the serological status of the chickens used. After challenge, the birds were observed for 14 days for mortality and clinical signs. Post-mortem examination was performed on all dead or euthanised birds and on all remaining birds after the observation period. At days 10 and 11 post challenge, 8 chickens per group were euthanised to evaluate respiratory signs based on the tracheal ciliary activity. Additionally, body weight was measured on day 0, before challenge and on day 35.

According to the challenge model study, the expected proportion of unvaccinated birds showing typical signs of respiratory disease (based on the tracheal ciliary activity assessment) following challenge with the virulent aMPV is $p0$=0.07. The vaccine complies with the test if statistically significant differences in the proportion of chicks with respiratory signs (based on the tracheal ciliary activity assessment) are found between vaccinated and control groups. Regarding the interference of the MDAs with the efficacy of the vaccine, the levels of percentage protection were similar to that obtained in chickens of the same age but vaccinated in the absence of MDAs.

<u>The following studies were performed to assess the influence of maternal antibodies on the efficacy of the vaccine</u>:

In the study performed by spray administration at one day of age in short-lived chickens, two groups (A and C) of 33 1-day-old short-lived SPF (MDA-) chickens and two groups (B and D) of 33 1-day-old short-lived commercial chickens with MDA were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to groups A and B by the oculonasal route. Groups C and D were mock-vaccinated with clean, fresh,

antiseptic and disinfectant-free water. The chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 100% of the non-vaccinated/challenged control groups (C and D) showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 75% in MDA- (group A) and 87.5% in MDA+ (group B) chickens (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. The vaccinated MDA+ group B and the vaccinated MDA- group A showed similar protection levels.

Regarding serology, representative ELISA titres were found in 1-day-old commercial chickens. At the time of challenge, all control and vaccinated chickens were seronegative. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge.

In the study by drinking water administration at 7 days of age in short-lived chickens, two groups (A and C) of 33 1-day-old short-lived SPF (MDA-) chickens and two groups (B and D) of 33 1-day-old short-lived commercial chickens with MDA were used. A vaccine dose of $10^{1.8}$ $CCID_{50}$ was administered to groups A and B by drinking water. Groups C and D were mock-vaccinated with clean, fresh, antiseptic and disinfectant-free water. The chickens were challenged with virulent aMPV at 21 days post vaccination. The challenge was valid as 87.5 and 100% of the non-vaccinated/challenged control groups (C and D, respectively) showed typical signs of respiratory disease (based on the tracheal ciliary activity assessment). The level of percentage of protection after challenge was 100% in MDA- (group A) and in MDA+ (group B) chickens (based on the tracheal ciliary activity assessment). The vaccine virus complied with the test as statistically significant differences in the proportion of affected chicks were found between vaccinated and control groups. The vaccinated MDA+ group B and the vaccinated MDA- group A showed similar protection levels.
Regarding serology, representative ELISA titres were found in 1-day-old commercial chickens, which already dropped at the time of vaccination on day 7. At the time of challenge, all control and vaccinated chickens were seronegative. Fourteen days after challenge, all birds showed a high titre of aMPV-specific antibodies. Regarding clinical signs, macroscopic lesions and body weight, no statistically significant differences were observed between vaccinated chickens and correspondent controls after the challenge.

It was concluded that vaccination by the recommended routes, with a dose of the minimum content or below recommended in the SPC, was efficacious and met the efficacy requirements including MDA-positive chickens.

Interactions

No studies on interactions were performed. Therefore, the following statements are included in SPC sections 3.8 and 5.1:

3.8 Interaction with other medicinal products and other forms of interaction:

"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."

5.1 Major incompatibilities

"Do not mix with any other veterinary medicinal product."

Clinical trials

Four GCP-compliant, multi-centred, randomised and double-blinded clinical field trials were carried out in commercial chickens in two different EU countries using both the oculonasal (spray) and the drinking water routes:

Study title	Admini-stration route/age	Titre adm. ($CCID_{50}$/ds)
Safety and efficacy assessment under field conditions of Respivac TRT vaccine in chickens (**future hens**) by drinking water.	Drinking water/ 7 days	$10^{3.5}$
Safety and efficacy assessment under field conditions of Respivac TRT vaccine in chickens (**future hens**) by spray.	Spray/ 1 day	$10^{3.49}$
Safety and efficacy assessment under field conditions of Respivac TRT vaccine in chickens (**broilers**) by drinking water.	Drinking water/ 7 days	$10^{3.5}$
Safety and efficacy assessment under field conditions of Respivac TRT vaccine in chickens (**broilers**) by spray.	Spray/ 1 day	$10^{3.5}$

Detailed background information on the field studies is provided in the summarised study descriptions in the safety part.

In summary, the chickens were vaccinated at the minimum age, i.e. 1 day old (via spray) or 7 days old (via drinking water), with a commercial dose of Respivac TRT or a comparator vaccine commercially available. The chickens were observed for 40 days (broilers) or 63 days (future hens) for safety signs such as adverse events, mortality rate and body weight. Regarding efficacy, birds would have been examined during a respiratory outbreak for mortality rate, respiratory clinical signs, final body weight and feed conversion rate (FCR). The serological data on day 0 show that the commercial bird flocks had representative levels of maternal antibodies (mean ELISA titres on day 0 ranged from 968.54 to 1752.54).

In the study performed by drinking water, in France, two groups of approximately 26,350 7-day-old future broiler breeders were used. A vaccine dose of $10^{3.5}$ $CCID_{50}$ was administered to group B via drinking water. Group A was vaccinated via drinking water with a commercial dose of a comparator vaccine. Vaccines against other avian diseases were simultaneously administered.

In the study performed by spray, in France, two groups of approximately 22,348 1-day-old future broiler breeders were used. A vaccine dose of $10^{3.49}$ $CCID_{50}$ was administered to group B via spray administration. Group A was vaccinated via spray administration with a commercial dose of a comparator vaccine. Vaccines against other avian diseases were simultaneously administered.

In the study performed by drinking water, in Belgium, two groups of approximately 71,212 7-day-old broiler chickens were used. A vaccine dose of $10^{3.5}$ $CCID_{50}$ was administered to group B via drinking water. Group A was not treated. Vaccines against other avian diseases were simultaneously administered.

In the study performed by spray, in Belgium, two groups of approximately 189,700 1-day-old broiler chickens were used. A vaccine dose of $10^{3.5}$ $CCID_{50}$ was administered to group B via spray administration. Group A was not treated. Vaccines against other avian diseases were simultaneously administered.

No respiratory outbreak of aMPV was reported during the follow-up of any of the studies performed

despite of the fact that the locations chosen are located in endemic areas. Therefore, it was not possible to evaluate the efficacy of the vaccine in target animals under field conditions. As the pre-clinical studies fully support the claims made in the summary of product characteristics (with the requested amendments), it is considered acceptable, based on Regulation 2019/6 Annex II as amended and the Guideline on clinical trials for immunological veterinary medicinal products (EMA/CVMP/IWP/260956/2021), not to further assess efficacy under field conditions.

Overall conclusion on efficacy

The applicant adequately demonstrated the efficacy of the vaccine.

The results from 8 laboratory (and 4 field) trials show that the product is effective for the active immunisation of chickens via the oculonasal route from one day of age and via drinking water from 7 days of age at the proposed dose of $\geq 10^{1.8}$ $CCID_{50}$ to reduce the detrimental effect caused by virulent avian metapneumovirus on the ciliary activity, which may be manifested in respiratory clinical signs.

Onset of immunity

Onset of immunity has been demonstrated at 3 weeks post vaccination.

Based on the results of the presented studies, the proposed claims could only be supported regarding the detrimental effect on the ciliary activity resulting from the infection by virulent avian metapneumovirus, which may be manifested in respiratory clinical signs. Section 3.2 of the SPC has been amended accordingly.

Duration of immunity

The duration of immunity has been adequately demonstrated up to 9 weeks post vaccination.

Duration of the protection of 9 weeks of the initial one-single dosage programme claimed for Respivac TRT has been satisfactorily demonstrated in the worst-case scenario (the minimum recommended ages). Since revaccination with a single dose of Respivac TRT during laying would not involve a different dose of administration from that confirmed in the duration of protection studies, the efficacy of revaccination is also demonstrated.

Maternally derived antibodies (MDA)

It has been adequately demonstrated that MDA do not interfere with vaccination.

The presented studies support the proposed claims regarding the detrimental effect on the ciliary activity in vaccinated chickens with MDA.

Interactions

No studies on interactions were performed. Appropriate statements are included in SPC sections 3.8 and 5.1.

Clinical trials

Four clinical studies, performed to evaluate the safety and the efficacy of the vaccine under field conditions, were carried out in two different EU countries (France and Belgium). No respiratory outbreak of aMPV was reported during the follow-up of any of the studies performed. Therefore, it was not possible to evaluate the efficacy of the vaccine in target animals under field conditions. However, according to the Regulation in force, this is considered acceptable since the intended claims are fully supported by the pre-clinical studies presented.

Part 5 – Benefit-risk assessment

Introduction

Respivac TRT is a lyophilisate for oculonasal suspension or for use in drinking water, intended to be used in chickens. Each dose of Respivac TRT contains $10^{1.8}$ - $10^{5.4}$ $CCID_{50}$ of live avian metapneumovirus subtype B, strain 1062.

At the time of submission, the applicant applied for the following indication:

"Active immunisation of chickens to reduce the respiratory signs caused by virulent avian metapneumovirus."

This was eventually modified in: *"Active immunisation of chickens to reduce the detrimental effect caused by virulent avian metapneumovirus on the ciliary activity, which may be manifested in respiratory clinical signs."*

The vaccine is contained in Type I glass vials of 10 ml containing 1,000 doses, 2,000 doses, 5,000 doses, or 10,000 doses of lyophilisate and in cardboard boxes of 1 or 10 vials.

The dossier was submitted in line with the requirements of Article 8 of Regulation (EU) 2019/6 (full application).

Benefit assessment

Direct benefit

The proposed benefit of Respivac TRT is its efficacy of active immunisation of chickens to reduce the detrimental effect caused by virulent avian metapneumovirus on the ciliary activity, which may be manifested in respiratory clinical signs. This benefit was shown in a large number of appropriately designed and well executed pre-clinical studies.

Respivac TRT can be applied at an early age of the birds (1-day-old) at the hatchery to provide protection against early replication of virulent aMPV and, thus, reduces clinical signs in case of infection. Consequently, the incidence of clinical signs and lesions in chickens, sometimes associated with high morbidity and occasionally higher mortality, is reduced, particularly when secondary infections are involved.

The onset of immunity against aMPV was established at 3 weeks post vaccination. The duration of protection is adequately demonstrated to be 9 weeks.

Clinical studies were performed to evaluate the safety and the efficacy of the vaccine under EU field conditions. No respiratory outbreak of aMPV was reported during the follow-up of any of the studies performed. Therefore, it was not possible to evaluate the efficacy of the vaccine in target animals under field conditions. Nevertheless, this is acceptable based on current regulation and the influence of maternally derived antibodies on the efficacy of the vaccine was investigated in well-designed laboratory studies, using commercial broiler chickens with confirmed MDA against aMPV.

Additional benefits

Respivac TRT is easy to apply to chickens from one day of age by spray vaccination or to chickens from 7 days of age by drinking water. Therefore, direct handling of birds can be avoided.

One single vaccination is sufficient to stimulate immunity against a relevant poultry pathogen. The vaccine strain was shown to be apathogenic to other susceptible avian species, limiting the risk to the environment.

Repeated vaccination every 9 weeks and throughout the reproductive phase is possible.

Respivac TRT increases the range of available treatment possibilities for the active immunisation of chickens against infections with aMPV.

Risk assessment

The main potential risks are identified as follows:

Quality

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Safety

Risks for the target animal

The product is generally well tolerated in the target animal when administered in accordance with the SPC recommendations. No adverse reactions were observed after a tenfold overdose of Respivac TRT administered by the oculonasal route by spray. The combined overdose and repeated dose study did not include any group to evaluate the administration via drinking water. However, spray administration is considered as the more critical route concerning the development of adverse reactions. In two clinical studies, chicken flocks were vaccinated with a standard dose via drinking water. No clinical signs or deaths related to the vaccination were noted in the two studies. Therefore, the approach of the applicant is acceptable.

Reproductive performance was assessed with birds in lay but no repeated dose was administered. Additional information was provided from the combined overdose and repeated dose study concerning necropsies and the evaluation of the reproductive tract which give assurance that a repeated vaccination will be safe during lay.

The biological properties were demonstrated in the provided studies. The vaccine strain is able to spread to unvaccinated chickens and turkeys in contact. Reversion to virulence was also investigated, and the results showed no potential risk. The chance of recombination with other strains or other viruses is considered to be effectively zero.

Risk for the user

The aMPV strain 1062 is non-pathogenic to humans and infects only avian hosts without causing clinical disease. The excipients used in this product are no risk for the user.

The lyophilisate is provided in glass vials. Skin or eye contact may occur due to spillage during reconstitution or administration. The SPC contains appropriate warnings and information.

The user safety for this product is assumed to be acceptable when used according to the revised SPC recommendations.

Risk for the environment

The vaccine virus is shed with respiratory excretions and can remain in the environment for some time.

Spread to chickens and turkeys was observed. In general, aMPV can only infect avian species. Appropriate measures mitigating the risk of spread of the vaccine strain to turkeys are included in the SPC.

Respivac TRT is not expected to pose a risk for the environment when used according to the SPC recommendations.

Risk for the consumer:

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

Risk management or mitigation measures

The following measures are included in the SPC to minimise the above-mentioned risks:

- The vaccine strain is excreted by chickens for at least 21 days.
- The vaccine strain may spread. Appropriate veterinary and husbandry measures should be taken to avoid spread of the vaccine strain to unvaccinated chickens and turkeys and other susceptible species.
- The veterinary medicinal product is subject to veterinary prescription.
- The personal protective equipment is specified.
- The vaccine strain can be found in the environment for at least 21 days. Adequate hygiene measures are recommended in the SPC.

Evaluation of the benefit-risk balance

The following indication which was considered acceptable by the CVMP is:

"Active immunisation of chickens to reduce the detrimental effect caused by virulent avian metapneumovirus on the ciliary activity, which may be manifested in respiratory clinical signs."
The claim was supported in the studies regarding the detrimental effect resulting from the infection by virulent avian metapneumovirus on the ciliary activity, which may be manifested in respiratory clinical signs. Section 3.2 of the SPC has been amended accordingly.

Onset of immunity is adequately supported by data. Duration of immunity is accepted to be 9 weeks. The influence of maternal antibodies on the efficacy of the vaccine against aMPV was studied using commercial broiler chickens with confirmed levels of MDA against aMPV.

Information on development, manufacture and control of the active substance and finished product has been presented and leads 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 is considered positive.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Respivac TRT is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EU) 2019/6).

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