7 September 2023
EMA/428105/2023
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Prevexxion RN+HVT (EMEA/V/C/006146/0000)

Vaccine common name: Marek's disease vaccine (live recombinant)

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 Boehringer Ingelheim Vetmedica GmbH submitted, on 28 September 2022, an application for a marketing authorisation to the European Medicines Agency (The Agency) for Prevexxion RN+HVT, through the centralised procedure under Article 42(2)a of Regulation (EU) 2019/6 (mandatory scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 15 June 2022 as Prevexxion RN+HVT has been developed by means of a biotechnological process, i.e. using recombinant DNA technology (Article 42(2)(a)(i)).

At the time of submission, the applicant applied for the following indications: for active immunisation of one-day-old chicks to prevent mortality and clinical signs and reduce lesions caused by Marek's disease (MD) virus (including very virulent MD virus).

Onset of immunity: 5 days after vaccination.

Duration of immunity: a single vaccination is sufficient to provide protection for the entire risk period.

Prevexxion RN+HVT has two live, cell-associated Marek's disease viruses (recombinant serotype 1, strain RN1250 and serotype 3, strain HVT FC126). The target species is chickens.

Each 0.2 ml dose of Prevexxion RN+HVT contains 2.9 to 3.9 $\log_{10}$ PFU (plaque forming unit) of serotype 1, strain RN1250 and 3.0 to 4.0 $\log_{10}$ PFU of serotype 3, strain HVT FC126. The product is presented in glass ampoules containing 1000, 2000 or 4000 doses.

The rapporteur appointed is Frédéric Klein and the co-rapporteur is Esther Werner.

The dossier has been submitted in line with the requirements for submissions under Article 20 of Regulation (EU) 2019/6 – a combination veterinary medicinal product application.

On 7 September 2023, the CVMP adopted an opinion and CVMP assessment report.

On 24 October 2023, the European Commission adopted a Commission Decision granting the marketing authorisation for Prevexxion RN+HVT.

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

Manufacturer of the active substance

Boehringer Ingelheim Animal Health France SCS
Laboratoire Porte des Alpes
Rue de l'Aviation
69800 SAINT PRIEST
FRANCE

Manufacturers of finished product

Sites in the EEA

Manufacturing and primary packaging of frozen vaccine:

Boehringer Ingelheim Animal Health France SCS
Laboratoire Porte des Alpes
Rue de l'Aviation
69800 SAINT PRIEST
FRANCE

Manufacturing and primary packaging of solvent:

Laboratoire BIOLUZ
Zone Industrielle de JALDAY
64500 SAINT JEAN DE LUZ
FRANCE

Secondary packaging frozen vaccine:

Boehringer Ingelheim Animal Health France SCS
Chemin de Cruzols
69210 LENTILLY
FRANCE

Secondary packaging solvent:

Laboratoire BIOLUZ
Zone Industrielle de JALDAY
64500 SAINT JEAN DE LUZ
FRANCE

or

Boehringer Ingelheim Animal Health France SCS
Chemin de Cruzols
69210 LENTILLY
FRANCE

Batch release site frozen vaccine

Boehringer Ingelheim Animal Health France SCS
Laboratoire Porte des Alpes
Rue de l'Aviation
69800 SAINT PRIEST
FRANCE

Batch release site solvent

Laboratoire BIOLUZ
Zone Industrielle de JALDAY
64500 SAINT JEAN DE LUZ
FRANCE

or

Boehringer Ingelheim Animal Health France SCS
Laboratoire Porte des Alpes
Rue de l'Aviation
69800 SAINT PRIEST
FRANCE

GMP certificates

Boehringer Ingelheim (St-Priest)

A GMP certificate issued by the French competent authorities is available in EudraGMDP. The certificate was issued on 04/10/2022, referencing an inspection on 10/06/2022. EudraGMDP document reference number 22-322724.

Laboratoire BIOLUZ

A GMP certificate issued by the French competent authorities is available in EudraGMDP. The certificate was issued on 11/01/2022, referencing an inspection on 28/10/2021. EudraGMDP document reference number 22-308331.

Boehringer Ingelheim (Lentilly)

A GMP certificate issued by the French competent authorities is available in EudraGMDP. The certificate was issued on 22/09/2022, referencing an inspection on 07/07/2022. EudraGMDP document reference number 22-322443.

All sites involved in the manufacturing of both the active substances and the final product, as well as the site for batch release of the final product, have been inspected and have valid GMP certificates in EudraGMDP.

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 substances 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

Prevexxion RN+HVT is a vaccine concentrate and consists of a frozen viral suspension containing two active substances in excipients without adjuvant, a live recombinant Marek's disease virus serotype 1 (RN1250 component, 2.9 to 3.9 $\log_{10}$ PFU per dose) and a live Marek's disease virus serotype 3 (HVT FC126 component, 3.0 to 4.0 $\log_{10}$ PFU per dose), both viruses being cell-associated. The vaccine concentrate is to be diluted in an aqueous solvent.

The excipients of the frozen cell-associated viral suspension are dimethyl sulfoxide, 199 Earle medium, sodium hydrogen carbonate, hydrochloric acid and water for injections. The excipients of the solvent are sucrose, casein hydrolysate, dipotassium phosphate, potassium dihydrogen phosphate, phenol red, sodium hydroxide or hydrochloric acid and water for injections.

Container and closure system

Frozen viral suspension

The vaccine is filled in Type I (Ph. Eur compliant) glass ampoules of 2 ml (1000 and 2000 dose presentations) or 5 ml (4000 dose presentation), which are sealed using a flame. Ampoules are sterilised by dry heat before filling, in compliance with Ph. Eur. The filled ampoules are stored in carriers (5 vials of 2 ml or 4 vials of 5 ml per carrier) which are firstly stored in canisters and these canisters are then stored in the liquid nitrogen containers.

Solvent

The solvent is filled into Polyvinylchloride (PVC) bags. The bags are manufactured by extrusion from sheets of PVC compliant with the requirements of the current Ph. Eur. edition. The bags are sterilised by steam sterilisation. The solvent can be filled into PVC bags of different sizes and with different volumes depending on the presentations:

Presentation (nominal volume)	Bag size
200 ml	250-ml bag
400 ml	500-ml bag
600 ml	1,000-ml bag
800 ml	1,000-ml bag
1,000ml	2,000-ml bag
1,200 ml	2,000-ml bag
1,600 ml	2,000-ml bag
1,800 ml	2,000-ml bag
2,400 ml	3,000-ml bag

Each bag is placed in a protective overpouch.

Product development

An explanation and justification for the composition and presentation of the vaccine has been provided.

Frozen viral suspension

Boehringer Ingelheim Animal health (BIAH) already owns marketing authorisations for a bivalent vaccine as well as monovalent vaccines against Marek's disease (MD): Cryomarex Rispens+HVT, Cryomarex Rispens and Cryomarex HVT. They contain one or two active substances, which correspond to the attenuated live Marek's disease virus (MDV), serotype 1, Rispens strain (CVI988) and/or attenuated live Marek's disease virus (MDV), serotype 3, HVT wild type strain (FC126).

Recently, BIAH has developed three new vaccines under the same project . Amongst them, two are already centrally authorised in the EU since July 2020 under the tradenames Prevexxion RN and Prevexxion RN+HVT+IBD. They contain RN1250 strain with or without vHVT013-69 strain; the latter being the active ingredient of Vaxxitek HVT+IBD (another BIAH centrally authorised vaccine against MD and infectious bursal disease). Prevexxion RN+HVT is the bivalent last developed vaccine herewith under assessment. This third vaccine is a live vaccine intended for mass vaccination by subcutaneous administration to one-day-old chicks, against Marek's disease induced by very virulent MD viruses or of lower pathogenicity. It is composed of two active substances (i.e. RN1250 and HVT FC126 strains).

RN1250 is routinely produced in EU since its approval (July 2020).

HVT FC126 is routinely produced in EU since many years because of its use in Cryomarex Rispens+HVT and Cryomarex HVT vaccines.

Choice of the vaccine strains

RN1250 strain

The MDV serotype 1 strain, RN1250 was originally generated and tested at the USDA ARS, Avian Disease Oncology Laboratory (ADOL) in the USA before being transferred to the applicant's Research and Development (R&D) facilities. RN1250 strain has been constructed by genetic engineering to generate a Marek's disease virus, serotype 1 (MDV1), strain CVI988 containing a long terminal repeat (LTR) sequence of a reticuloendotheliosis virus (REV).

Thus, RN1250 strain includes genomic parts:

- from the currently most efficacious and safe vaccine MDV strain: the CVI988 Rispens strain
- from the MDV RM1 strain, derived from a virulent MDV strain (JM/102W) in the genome of which two copies of REV LTR were inserted
- from the very virulent MDV Md5 strain, in which a fragment of MDV RM1 strain containing the REV LTRs was inserted.

HVT FC126

The HVT FC126 strain is known as the parental strain used for generation of recombinant strains (for example: vHVT013-69 strain used in Vaxxitek HVT+IBD). It was originally isolated from turkeys' blood, then cultured first on duck fibroblasts and then on SPF chicken embryo fibroblasts, finally used as a vaccine strain in the commercialised products Cryomarex HVT and Cryomarex Rispens+HVT.

Combination of the two strains

The HVT-based vaccines protect well the chickens against vMDV challenge but their efficacy against vvMDV and vv+MDV is limited. The best MD vaccine used so far in Europe, and able to protect against both vvMDV and vv+MDV, is based on the CVI988 (Rispens) strain (Witter et al., 2005). This strain is often used in combination with parental or recombinant HVT. Indeed, in the field, the most common vaccine used in layer and breeder chicks, in several countries, for many years, has been a bivalent combination of HVT and Rispens (Dunn and Gimeno, 2013; Baigent et al. 2006). The benefit of this combination is to achieve a better early protection than the monovalent vaccines against vvMDV

strains demonstrated by Geerligs et al. (1999). As the addition of HVT to serotype 1 vaccine is beneficial for MD protection, combining both vaccine strains (i.e. RN1250 and HVT) allows the users to protect their chicken flocks against one important disease requiring an early onset of protection with a single injection from a vaccine ampoule containing these two vaccine viruses.

Choice of AI quantification method

Both RN1250 and HVT FC126 active substances are titrated in the finished product according to the induction of a cytopathic effect revealed in the form of foci (Plaque Forming Units - PFU) after inoculation on chicken embryo fibroblasts, as classically done for Marek's vaccines. PFU are revealed by indirect immunofluorescence using specific monoclonal antibodies. The technique used was fully validated.

Choice of the starting materials of animal origin

Starting materials of animal origin have been used only for the virus production. They were treated by gamma radiation when relevant. The gamma radiation of these starting materials was validated.

All starting materials of animal origin used in the production process of Prevexxion RN+HVT vaccine were assessed regarding their risk for transmission of TSE. It is concluded that they comply with the current regulatory requirements and that all necessary measures have been taken to minimise any TSE risk. The overall risk is therefore considered to be negligible.

All starting materials of animal origin used in the production process of Prevexxion RN+HVT vaccine were also assessed regarding their compliance to the requirements of Ph. Eur. 5.2.5. "Management of extraneous agents in immunological veterinary medicinal product". A comprehensive review of the risks and control measures in place for each starting material has been performed.

Finished product presentation

The vaccine is presented in the form of a sealed glass ampoule containing the frozen antigen suspension. The vaccine is to be diluted in the solvent presented in PVC bags used for the preparation of cell-associated poultry vaccines.

Three presentations are proposed:

- a 1000 dose presentation corresponding to 2 ml antigen suspension to be diluted in 200 ml solvent for a subcutaneous use,
- a 2000 dose presentation corresponding to 2 ml antigen suspension to be diluted in 400 ml solvent for a subcutaneous use,
- a 4000 dose presentation corresponding to 4 ml antigen suspension to be diluted in 800 ml solvent for a subcutaneous use.

Definition of the specifications

For RN1250: The minimum protective dose was set at 2.9 $\log_{10}$ PFU/dose, according to the results of the efficacy studies. The maximum release dose was set to 3.9 $\log_{10}$ PFU/dose, as supported by the safety studies. The minimum release titre is sufficient to cover the loss during shelf life demonstrated during real-time stability studies.

For HVT FC126: The minimum protective dose was set at 3.0 $\log_{10}$ PFU/dose, according to the results of the efficacy studies. The maximum release dose was set to 4.0 $\log_{10}$ PFU/dose, as supported by the safety studies. The minimum release titre is sufficient to cover the loss during shelf life demonstrated during real-time stability studies.

Batches used in clinical trials were described (including their antigen content) and batch certificates were provided.

Storage conditions and shelf life

To guarantee a satisfactory stability for the proposed shelf life of 36 months, as demonstrated in the stability study of the vaccine conducted on batches over at least 39 months of storage, the vaccine must be stored in liquid nitrogen protected from light. Storage in liquid nitrogen is known to be particularly favourable for these viruses, which must remain associated to the cells used for virus production. The vaccine diluted in its solvent can be stored for two hours at room temperature (below 25°C) as demonstrated in the in-use stability study conducted on batches.

Choice of excipients

One of the vaccine excipients, dimethyl sulfoxide (DMSO), was selected for its capacity to protect cells infected by the vaccine viruses during freezing.

Solvent

The solvent is a saline solution supplemented with different substances which act as a nutritive component (sucrose), protective agent during the dilution of the vaccine (casein hydrolysate), osmolarity agents (sucrose, potassium hydrogen, dipotassium phosphate) or are used to adjust the pH (hydrochloric acid, sodium hydroxide). The phenol red acts as an indicator of whether the pH is within the release specifications.

Choice of containers

The container constituent (polyvinylchloride bag) was chosen for its pharmaceutical quality and compliance with the Ph. Eur. requirements. Furthermore, this material, being heat-resistant, is appropriate for steam sterilisation.

Description of the manufacturing method

RN1250 component

The active substance is a suspension of MDV SR-1 RN1250, multiplied in SPF chicken embryo cells. A seed lot system is used for its preparation. Batches of active substance are produced from maximum 5 passages of the master seed virus (MSV) in SPF chicken embryo cells. After incubation of chicken embryo cells with virus, when, according to the applicant, the cytopathic effect caused by the virus is optimum, the cells are harvested, centrifuged, diluted with serum and sieved. For the cell detachment taking place during harvest, appropriate enzymes are used. The cell suspension constitutes a batch of active substance.

HVT FC126 component

The active substance is a suspension of HVT FC126 virus, multiplied in SPF chicken embryo cells. A seed lot system is used for its preparation. Batches of active substance are produced from maximum 5 passages of the master seed virus (MSV) in SPF chicken embryo cells. After incubation of chicken embryo cells with the virus, when the cytopathic effect caused by the virus is optimum, the cells are harvested, centrifuged, diluted with serum and sieved. For the cell detachment taking place during harvest, appropriate enzymes are used. The cell suspension constitutes a batch of active substance.

Frozen viral suspension

The formulation is based on volume. The active substances, RN1250 and HVT FC126, are mixed and stirred. DMSO is mixed with dilution medium and added to the active substances under stirring. The bulk product is filled into sterilised ampoules. Ampoules are subsequently sealed using a flame. Filled ampoules are frozen in a controlled manner and stored in liquid nitrogen.

Solvent

The different excipients of the solvent (sucrose, casein hydrolysate, dipotassium phosphate, potassium dihydrogen phosphate) are blended and stirred. After the addition of phenol red and of water, the pH is adjusted using NaOH or HCl. Then, water is added to reach the final volume. The bulk obtained is maintained under stirring until filling. The bulk product is filled into containers that are already labelled. A terminal sterilisation process is used after the filling step. Bags are then stored at room temperature. Then, each bag is placed in a protective overpouch. Immediately after addition of the overpouch, the secondary packaging is carried out. After secondary packaging, the solvent is stored at room temperature.

All steps of the manufacturing process have been validated. It has been demonstrated that the manufacturing process is capable of producing finished product of the intended quality in a reproducible and consistent manner. The in-process controls are adequate for this type of manufacturing process.

Production and control of starting materials

Detailed information and certificates of analysis were provided for all starting materials listed in Ph. Eur. demonstrating compliance with the relevant monographs.

Starting materials not listed in a pharmacopoeia were described in detail. Adequate information was provided on the culture media composition and components.

RN1250 master seed virus

RN1250 is an engineered Marek's disease virus based on the MDV CVI988 parental vaccine virus that contains two copies of reticuloendotheliosis virus (REV) long terminal repeats (LTR) from MDV RM1 strain inserted in its genome. The RN1250 recombinant virus was generated by in-vitro homologous recombination between CVI988 and a cosmid containing a genomic fragment of RM1 and of Md5 MDV1 strains. The sequence analysis confirmed that the RN1250 selected clone is a virus containing MDV genomic segment from three different MD viruses: CVI988, RM1 and Md5.

The MSV was qualified using the following tests: bacterial and fungal sterility, mycoplasma, identity, virus titre and viral purity by a combination of tests and satisfactory risk assessment complying with the requirements of Ph. Eur. 5.2.5. The working seed virus (WSV) is obtained from the MSV by carrying out passages in SPF chicken embryo cells. The WSV was qualified using the following tests: bacterial and fungal sterility, mycoplasma, identity and virus titre. Both the MSV and WSV are stored frozen in liquid nitrogen.

The genetic stability of RN1250 was evaluated by comparing the genome structure of the RN1250 MSV with that of RN1250 passaged in CEF cell cultures or in chickens. Results of different molecular biology techniques showed no difference between the in-vitro and in-vivo passaged viruses and the MSV, indicating RN1250 genetic stability.

HVT FC126 master seed virus

The HVT FC126 strain was isolated in 1968 by R.L. Witter et al. (Regional Poultry Research Laboratory (RPRL) of East-Lansing, U.S.A.) from blood samples collected on a flock of turkeys. The strain isolated was passaged in duck fibroblasts. Infected cells from the last passage were filled in ampoules and subsequently stored in liquid nitrogen. From this passage, several passages in chicken embryo cells were carried out, and the harvest of the last passage was filled in ampoules and frozen in liquid nitrogen to constitute the MSV.

The MSV was qualified using the following tests: bacterial and fungal sterility, mycoplasma, identity, virus titre and viral purity by a combination of tests and satisfactory risk assessment complying with the requirements of Ph. Eur. 5.2.5. The WSV is obtained from the MSV by carrying out passages in SPF chicken embryo cells. The WSV was qualified using the following tests: bacterial and fungal sterility, mycoplasma, identity and virus titre.

TSE risk assessment

For all starting materials of biological origin including the MSV of both active substances, a TSE risk assessment has been provided. The overall conclusion of the applicant that the risk of TSE transmission has been minimised as far as possible is supported.

Control tests during the manufacturing process

Frozen viral suspension

Cultures and harvests are visually inspected. The cell counts of the active substances RN1250 and HVT FC126 are determined and if necessary, adjusted prior to blending. This cell count is measured on the intermediate cell suspension; this test is included as an in-process control.

Time is recorded during mixing and homogenising of active substances and excipients in the final formulation. Volume is measured during filling of finished product in vials. Filled vials are checked for appearance. During freezing of vials, time and temperature are recorded.

Solvent

Time is monitored during blending, sterilisation and drying. Osmolality and pH are measured at the level of the final bulk. Volume is measured during filling in bags. Terminal sterilisation is monitored. Temperature is recorded. The finished product is checked for appearance.

Control tests on the finished product

The description of the methods used for the control of the frozen cells suspension (RN1250 and HVT FC126 identity, RN1250 and HVT FC126 titration, visual appearance, pH, volume, bacterial and fungal sterility, mycoplasma and purity) and of the solvent (visual appearance, pH, volume, cryoscopic depression and bacterial and fungal sterility) were provided. For non-pharmacopoeial methods, validations were provided. The specifications proposed at release and at the end of shelf life are appropriate to control the quality of the finished product.

Briefly summarised, for titration of both active substances chicken embryo fibroblasts are incubated with the active substance. After induction of the cytopathic effect by the virus, the formed plaques are stained using immunofluorescence staining and the virus titre is calculated after counting of the stained plaques. Details on the antibodies used for staining as well as on the read-out and the calculation of the virus titre have been provided. Based on the data of the validation reports and the supplementary details on the specificity of the used antibodies and the robustness of the staining method the method is considered to be appropriately validated.

Based on the conclusion of the extraneous agents risk assessment according to the requirements of Ph. Eur. 5.2.5, appropriate validated purity testing is performed on the finished product.

The proposed finished product tests on the solvent are considered appropriate and have been satisfactorily described and validated, if applicable.

Batch-to-batch consistency

The applicant presented final product data for the manufacture of at least three consecutive final product batches (both frozen viral suspension and solvent). The results were compliant with the specifications.

Stability

No stability data were provided for the active substances, which is acceptable as they are not stored but immediately processed into finished product.

Frozen viral suspension

Long-term stability studies of the Prevexxion RN+HVT vaccine were carried out. The results show that the vaccine can be stored for 36 months in liquid nitrogen. Stability was monitored on batches stored during at least 39 months in liquid nitrogen. The vaccine batches were tested for physicochemical characteristics (appearance, pH, volume), sterility (bacterial and fungal, mycoplasma) and titration of RN1250 and HVT FC126 components. Appearance, pH, volume, sterility and titres remained conform to the acceptance criteria throughout the monitoring period. Therefore, the 36 months shelf life claimed for the vaccine is considered acceptable.

The in-use stability of the vaccine was evaluated after dilution of the thawed viral suspension in the solvent. Titration results show that the vaccine must be used within 2 hours at room temperature after dilution.

Solvent

The solvent has been used for decades to dilute all the applicant's cell-associated Marek's disease vaccines. The historical available results showed that this solvent can be stored for 36 months, at a temperature below 30°C. Nevertheless, following the recent change in the nature of the overpouch, a new stability study was conducted with batches representative of different presentations. This latest study is still on-going and will be conducted up to 36 months. In a conservative approach, the applicant proposed to temporarily decrease the solvent shelf life to 24 months, at a temperature below 30°C. These duration and storage condition were endorsed by the CVMP in October 2021.

Overall conclusions on quality

The applicant has adequately described the composition and development of the vaccine and its active substances. Detailed information is provided on the manufacturing process and on the tests performed during manufacture and on the finished product. Batch data and stability data are presented. Quality control of the starting materials is adequately performed. The certificate of analysis of a proposed supplier of one starting material should be provided when available. The RN1250 and HVT FC126 active substances are derived from the same seeds as those used in the registered vaccines Prevexxion RN and Prevexxion RN+HVT+IBD (for RN1250) and Cryomarex Rispens+HVT and Cryomarex HVT (for HVT FC126). Generation and qualification of the RN1250 virus seed and the HVT FC126 virus seed have been adequately described. Appropriate in-process control tests and control tests on the finished product for production of consistent batches of vaccine and the solvent are in place. Validation reports for the non-compendial analytical methods confirmed their validated state. The manufacturing process was shown to be properly validated. The stability data support the proposed shelf life of the finished product (frozen viral suspension) and the solvent. The in-use shelf life was also properly validated.

In conclusion, the quality part of the dossier can be approved. However, one post authorisation

measure has been identified.

POST-AUTHORISATION MEASURES

Recommendation:

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

- The certificate of analysis of a proposed supplier of one starting material should be provided as soon as available.

Part 3 – Safety documentation (safety and residues tests)

General requirements

Prevexxion RN+HVT is a bivalent vaccine containing two cell-associated live vaccine strains already authorised in several vaccines, an engineered Marek's disease virus (MDV-1) serotype 1 (GMO), named RN1250 strain, in combination with a turkey herpesvirus (HVT), named HVT FC126. The vaccine is intended for a single administration to one-day old chicks by subcutaneous (SC) injection (0.2 ml per bird) in order to prevent mortality and reduce clinical signs and lesions caused by Marek's disease virus (including very virulent MD virus).

Safety documentation

The data included in the dossier were generated in compliance with Regulation (EU) 2019/6, the Ph. Eur. general text 5.2.6. about veterinary vaccines and with the applicable requirements for recombinant organisms (Directive 2001/18/EC and 2009/41/EC). Requirements from the Ph. Eur. monograph 0589 for live Marek's disease vaccine have also been fulfilled, when applicable.

In all studies, the vaccine was administered by the SC route, as recommended. Pre-clinical studies were conducted to investigate the safety of the product. These included overdose, immune function and reproductive performance studies. Two clinical trials have also been submitted. The preclinical studies were reported to be GLP compliant, carried out in chickens of the minimum age recommended for vaccination (one day old) and by using production batches.

The methods used for the investigation of the vaccine safety (detection of the DNA of the two strains and detection of MDV antibodies) were validated for purpose of their use in the studies.

By referring to Art. 20 of Regulation (EU) 2019/06 about the combination of active substances already included in authorised vaccines, safety data about spread, dissemination, recombination and virulence of the vaccine strains have not been provided. This approach is acceptable because no results indicated that the combination of the strains does modify their genuine biological parameters.

For the impact on the immunological functions, the applicant has also referred to a study performed with another vaccine where the strain HVT FC126 was replaced by its derived GMO strain vHVT013-69, the biological characteristics of which were shown to be similar.

Pre-clinical studies

Since repeated two overdose studies were performed, no studies on the administration of one dose or on the repeated administration of one dose were undertaken. The conclusion of these two studies were included both in the sections 3.6. and 3.10 of the SPC.

Safety of one administration of an overdose

A first study was invalidated as some mistakes were done at final necropsy (non-systematic and non-standardized sampling). However, all the results collected before the necropsy did not raise any concern.

Another study was thus performed according to the same design compliant to Ph. Eur. 0589. One-day old SPF chickens were vaccinated with a 10x overdose of the vaccine according to the proposed vaccination scheme and monitored over 120 days; their body was weighted on D0 then at three occasions until D120. They were compared to chickens injected with only vaccine solvent. The chicken

breed was fully susceptible to Marek virus since more than 70% of another group of control birds got the disease after a challenge with a virulent MDV strain, as required by Ph. Eur. monograph 0589. The chicken breed was fully susceptible to Marek virus since 97% of a group of 40 control birds got the disease after a challenge with a virulent MDV strain. Birds were properly vaccinated since RN1250 and HVT FC126 vaccine strains were detected in the spleen of each vaccinated birds tested, while it was not detected in the controls tested. In the vaccinated and in the control groups, neither clinical signs nor mortality attributable to Marek disease were observed. No local reactions were noticed. The growth curve did not significantly differ between the 2 groups. In summary, in this study no lesions on the bursa of Fabricius conversely to the previous study nor lesions or clinical sign ascribable to Marek's disease or to the vaccine were detected leading to the conclusion that a 10X overdose of the vaccine was safe and complied with Ph. Eur. 0589 requirements.

Examination of reproductive performance

The impact on the reproductive performance has been investigated in a field trial already submitted for other authorised vaccines, where RN1250 associated with Cryomarex HVT were compared to an authorized vaccine with the same combinations of valences. The pullets of these 2 groups were monitored up to 77 weeks of age (whole production period), each one in a multiple-site production system of 2 farms.

The intake of the vaccine was confirmed as the vaccine strain RN1250 was amplified by PCR overall in 73% of the tested spleens in the vaccinated group.

No difference between vaccines on the quality and the number of eggs was reported in pullets vaccinated according to the proposed SPC, long before laying. The complete assessment of this study is reported in the Clinical trial section of this report.

In conclusion, the vaccine can be administered safely to future layers and a proper warning included in the SPC reminds that the vaccine is intended to be administered to one-day old chickens.

Examination of immunological functions

To demonstrate the possible impact of this vaccine on the immunological functions, the applicant has submitted a study already included in the dossier of other authorised vaccines. In the study, the RN1250 was combined with vHVT013, a recombinant strain derived from HVT FC126 in which a sequence coding the VP2 of IBDV was inserted. The applicant reasoning is that the 2 strains are similar and interchangeable when they are combined to RN1250 considering their MDV3 biological properties.

In this study, the efficacy of NDV vaccination at day 7 of birds previously vaccinated or not with the combination of strains RN1250 + vHVT013 or RN1250 alone on D0 was challenged. Both strains were at least at their maximal titres and NDV vaccine was at minimal one used according to its label. The chickens were challenged 2 weeks later with a virulent NDV strain (Herts). While 100% of NDV non-vaccinated birds were euthanised within 2 days, 100% of the vaccinated were protected regardless of whether they were beforehand vaccinated with RN1250 + vHVT013, RN1250 alone or not. The magnitude of ND seroconversion was similar in the three NDV vaccinated groups. In conclusion, the 2 vaccine strains did not impair the functioning of immune system as checked throughout its response to NDV vaccination.

Special requirements for live vaccines

By referring to Art. 20 of Regulation (EU) 2019/6 about the combination of active substances already included in authorised vaccines, safety data about spread, dissemination, recombination and virulence

of the vaccine strains have not been provided.

This is acceptable since no specific concerns were raised in the overdose studies of the combined vaccine to prompt to undertake specific investigations.

User safety

Prevexxion RN+HVT vaccine is a cell-associated live vaccine, which contains the herpesvirus of turkey strain HVT FC126 and the MDV-1 recombinant strain RN1250. In general, avian herpesviruses are not known to be a hazard to humans. Avian herpesviruses are not indicated in EU Directive 2000/54/EC on the protection of workers from risks related to exposure to biological agents at work. Moreover, the genetic modification of RN1250 have attenuated the genuine biological properties of the parental strain.

Prevexxion RN+HVT contains no adjuvant and no components which are expected to pose a risk for the user following accidental exposure.

The vaccine is filled in glass ampoules stored in liquid nitrogen, which might explode when removed from cold storage and thawed, leading to exposure or cuts by the glass. This risk is considered very low because these frozen ampoules are already very common in practice today and users are professionals well trained to handle this kind of vaccine.

The risk of accidental self-injection of the vaccine to the user when administered subcutaneously to one-day-old chickens is low as the users are trained professionals and the volume to be injected is small (0.2 ml). The consequences of accidental self-administration are therefore negligible.

Pharmacovigilance for both RN1250 alone or in combination with vHVT013-69 has not reported human adverse event nor for HVT FC126 alone or in combination with the Rispens strain.

Finally, in sections 3.5 and 3.9 of the SPC the attention of the user of the vaccine is drawn on the potential risk of ampoule explosion and advice is given on how to handle the administration.

Prevexxion RN+HVT has thus an acceptable level of risks for the user when administered according to the SPC.

Study of residues

MRLs

Prevexxion RN+HVT is a bivalent vaccine which does not contain any adjuvant.
The components are either listed in table 1 of the annex of Commission Regulation No. 37/2010 as allowed substances for which no MRLs are required or considered as substances not falling within the scope of Regulation (EC) No. 470/2009 (e.g. active principles of biological origin intended to produce active immunity, used in IVMPs) with regard to residues of veterinary medicinal products in foodstuffs of animal origin.
For the media as well as phenol red, the data provided by the applicant were assessed and the substances considered not being pharmacologically active at the doses used.
Gentamicin is used in the manufacturing process and theoretical residues which might remain in the final product would be well below a pharmacologically active concentration.

Withdrawal periods

A withdrawal period of zero days is proposed.

Interactions

No claim for associated use is put forward and appropriate warnings are included in the SPC.

Clinical studies[1]

A clinical trial was performed in 2 French farms and included 4 flocks of long life broilers (4400 chicks per flock) that were vaccinated at one-day old at the hatchery with either Prevexxion RN+HVT or a commercial Rispens+HVT vaccine. Two flocks were then transferred into one of the farms and the two other flocks in the second farm. They were then monitored until slaughtering at week 12. The investigators were blinded throughout the trial.

The hatched chicks had MDV maternally derived antibodies. The intake of the vaccine was confirmed as the vaccine strain RN1250 was amplified by PCR overall in 80% of the spleens of the vaccinated groups sampled on day 8-9 and HVT FC126 in 100% of the tested birds.

The mortality rate was slightly higher for one of the breeds and the applicant has associated this higher mortality rate with higher heterogeneity of the birds; however, the rate was lower than the 1.5% threshold set by the investigator for both breeds.
The body weight gain was as good in the vaccinated birds as in the controls.
The feed intake, as well as feed conversion, were very similar between groups raised in the same farm, and between farms.
The number of slaughtered animals, as well as the number of condemned animals, were very similar between groups and no lesions suggestive of Marek's disease were observed.
Finally, historical performance data showed superior zootechnical results for all groups compared to previous flocks housed in both farms.
In conclusion, no safety concerns were raised under field conditions for long life broilers.

To support the safety in the layers, a clinical trial already assessed for the authorisation of other vaccines, has been provided because there were groups, which are relevant for the vaccine Prevexxion RN+HVT. In this trial, two flocks of about 10,000 pullet chicks were vaccinated subcutaneously either with RN1250 + Cryomarex HVT or a commercial Rispens+HVT vaccine at one day of age at the hatchery then settled in a pullet farm. From 18 weeks of age onwards, birds were transferred to a laying farm until slaughtering. They were monitored up to 77 weeks of age. The efficacy results are addressed in the Efficacy section of this report.
The vaccination was effective since RN1250 vaccine strain was found in 73% of the sampled chickens.
No immediate reactions after vaccination were reported as well as no MD clinical signs throughout their 77 weeks of life.
The mortality rates were lower or similar than historically anticipated before the laying phase (total mortality rate of 1.6% and 4.1% respectively in the group vaccinated with RN1250 + Cryomarex HVT and in the control group). During the laying phase, episodes of suffocation (mainly in the control group) jeopardized the results and no conclusion could be drawn.
No difference in body weight between vaccinates and their relative controls, were reported (18 weeks after vaccination and further on) nor was the feed intake different before the laying phase.
There were no differences on the quality (class A, decommissioned and destroyed) and the number of eggs.
In conclusion, Prevexxion RN+HVT had no impact on clinical and technico-economic results and no clinical signs suggestive of Marek's disease were reported.

[1] If relevant for safety.

Environmental risk assessment

The proposed vaccine is compliant with Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

The applicant has provided a detailed risk assessment of the combined vaccine containing both RN1250 and HVT FC126 viruses, in accordance with the EMA guidance (EMA/CVMP/074/95).

Hazards

Both vaccine strains were shown to infect/replicate only in susceptible birds but not in mammals. While they were found in feathers, no spread to susceptible contact chickens was shown.

The biological pattern of RN1250 strain was shown to be not very different from its parental strain and its genetic and phenotypic stability after serial passages in chickens was acceptable. Components, other than the vaccine strains, used to formulate the vaccine are classical components, used in many biological products, known for their absence of effect on the environment.

Furthermore, decades of administration of several billions doses for HVT FC126 strain as well as years and million doses of RN1250 have corroborated their absence of impact on the environment.

Taking all the risk factors into consideration, the level of risk to the environment of Prevexxion RN+HVT can be considered as negligible. Prevexxion RN+HVT is not expected to pose a risk to the environment when used according to the SPC.

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

The applicant has provided detailed information about the possible environmental risk of the current vaccine that contains a genetically modified virus.

The vector construction, vector elements, analytical test methods and vector characteristics including genetic stability, have been extensively described for the RN1250 virus strain. The recombinant virus does not contain any potentially harmful sequences. All sequences present in the vector also occur in naturally occurring viruses.

Information was provided on possible release of the GMO to the environment. The likelihood is considered very low. In case of spread, homologous recombination with other (wild type) herpesviruses cannot be excluded. However, such recombination events (if any) would result in viruses with the same characteristics as either the wild type variant or the vaccine virus; it cannot result in a more virulent strain. Besides birds, no other species are known to be infected with the vaccine viruses, which are non-pathogenic for humans. Consequently, there is no intrinsic risk for humans related to the current vaccine.

In conclusion, the overall risk of the current vaccine towards humans and the environment is considered negligible.

Overall conclusions on the safety documentation

The clinical safety of a 10X overdose of RN1250+ HVT FC126 vaccine was investigated in 2 studies performed in compliance with Ph. Eur. 0589 and neither adverse impact nor Marek-like signs or lesions were reported.

To rule out an impact on reproductive performance, the applicant showed in a field study that RN1250

+ HVT FC126 have no impact on the quantity and quality of laying in laying hens.

An already assessed study was included to support the absence of impact on the immune system where the strain vHVT013-69, which is a recombinant from HVT FC126, in association with RN1250 had no impact on Newcastle vaccine protection.

The studies exploring the biology of both strains were not included in the dossier based on Art. 20 of Regulation (EU) 2019/6. This is acceptable because the association of the 2 strains has no conspicuous impact on their own biology.

The conclusion of the user safety assessment is that the handling of vaccine ampoules frozen in liquid nitrogen and the risks of needle stick injuries are the main risks and adequate warnings have been included in sections 3.5 and 3.9 of the SPC.

An environmental risk assessment compliant with the EMA guidance and with Dir 2001/18/EC has concluded that the risk for the environment is negligible when the vaccine is used in accordance with the SPC.

Residues of the vaccine are not considered to represent a consumer safety concern; a withdrawal period of zero days is appropriate.

The safety profile was confirmed in a clinical trial with broilers and an already assessed trial with pullets where the vaccine was compared to already marketed vaccines. Neither adverse reactions nor worsening of zootechnical parameters were reported.

The vaccine is considered to be safe for the target species and non-target species, the user, the consumer and the environment.

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

General requirements

Prevexxion RN+HVT is a vaccine containing two cell-associated MDV strains already authorised alone or in combination with other vaccine strains. It is intended for active immunisation of healthy one-day-old chickens, by one single SC injection (0.2 ml per bird) in order to prevent mortality and reduce clinical signs and lesions caused by Marek's disease virus (including very virulent MD virus). Immunity is intended to be established from 5 days after vaccination and a single vaccination is sufficient to provide protection for the entire risk period.

The efficacy of the vaccine against Marek's disease was investigated in 2 preclinical and 2 clinical studies, one in long life broilers and the other in laying hens which has already been assessed for other authorised vaccines. The preclinical studies were conducted in compliance with Ph. Eur. 0589 when applicable and according to the proposed SPC. The clinical trials were conducted in compliance with GCP requirements. Industrial batches were used.

Challenge model

The studies were designed in compliance with requirements of Ph. Eur. monograph 0589 on Marek's disease vaccine (live).MD challenge was performed with two vvMDV-1 strains (RB1B and Md5) which are heterologous to the vaccine strain and representative of those which are spreading throughout Europe.

Efficacy parameters and tests

The parameters chosen are in line with the requirements of Ph. Eur. monograph 0589 and therefore considered appropriate for evaluating the efficacy of the product. Further methods used for the investigation of vaccine efficacy (detection of the DNA of the two strains and detection of MDV antibodies) were validated for purpose of their use in the studies.

Pre-clinical studies

Dose determination

No specific study on the determination of the vaccine dose has been performed but the proposed minimum dose has been evaluated in the efficacy laboratory studies. In summary, sufficient efficacy was demonstrated for a minimum dose of 2.9 log10 PFU/dose for RN1250 and 3.0 log10 PFU/dose for HVT FC126.

Onset of immunity

The MD protection afforded by RN1250 and HVT FC126 strains, at their minimum dose (2.9 log10 PFU and 3.0 log10 PFU respectively) was determined by a challenge with the vvMDV strain RB1B, 5 days after SC vaccination of SPF chickens at one day of age.
The birds were monitored over 70 days.

This study was compliant to Ph. Eur. 0589 since ≥ 70 % (87% in this trial) of the unvaccinated controls

contracted Marek disease and no mortality occurred before challenge. 86 % of the vaccinates were protected from Marek clinical signs and none died or got Marek specific lesions. Therefore, the vaccine complies with the test since the relative protection is ≥ 80 % (84 % in this trial).

It was concluded that vaccination with a minimum dose recommended in the SPC was efficacious and met the efficacy requirements from 5 days after vaccination when administered by SC route to one-day-old SPF chickens.

Due to 4 vaccinates with locomotor troubles, which were classified as MD clinically ill because no other diagnostic was able to be put forward and notwithstanding that no MD lesions were detected, the claim, different to the originally proposed one, "to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus)" is supported based on the results of the presented study.

Duration of immunity

The immunisation by herpesvirus such MDV is lifelong and only chicks are at risk of MDV infection. Therefore, it is accepted that no study has been undertaken to back the duration of MD immunity.

Maternally derived antibodies (MDA)

The protection against Marek's disease was assessed by challenge of conventional pullet chicks 6 days after vaccination.

Pullets were vaccinated at hatching (D0) with Prevexxion RN+HVT at the minimum dose and controls were left unvaccinated.

Pullets were born from breeders vaccinated according to a widespread vaccination program against Marek's disease (Rispens and HVT vaccine strains at D0) and thus MDA against MDV were found in all the sampled birds at hatching. Therefore, it is considered that their MDA level was representative and comparable to that currently found in the field.

The DNA of RN1250 and HVT FC126 vaccine strain was amplified in 100% and 80% of the vaccinated chickens sampled 7 days after vaccination which confirmed the vaccine take.

The intraperitoneal challenge with the vvMDV strain RB1B was done 6 days after vaccination. Eighty-three % of control birds died or were euthanised on ethical ground due to severe challenge-related clinical signs while all the other got MD gross lesions. Two vaccinates were euthanised on ethical ground and one got, at final necropsy, hypertrophied gonad classified as caused by MDV as worst-case scenario. The 91.4% absolute and relative protection result comply with Ph. Eur. 0589 requirements.

It was concluded that vaccination by the recommended route with a minimum dose as recommended in the SPC was efficacious and met the efficacy requirements, including in MDA positive animals.

Due to two vaccinates with severe challenge-related clinical signs found, the acceptable claim is "to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus)". This claim is appropriately supported by the results of the presented study.

Interactions

No interaction studies have been conducted. Respective standard warnings are included in sections 3.8 and 5.1 of the SPC.

Clinical trials

A clinical trial was undertaken in 2 French farms; for detailed description of this study and the results associated with the safety of Prevexxion RN+HVT see the clinical study section in the safety part of this report. Maternally derived antibodies were detected on day 1 at hatchery against MDV, which confirmed the conventional status of the chicks whose parental hens were vaccinated with a combination of a Rispens and a HVT vaccine at hatching. The MDA level of the used chicks is considered to be comparable to that currently found in the field. Because no clinical signs suggestive of Marek's disease were anticipated to occur in the farms during the study, some birds were taken from the hatchery to be challenged in laboratory by virulent MD strain at the onset of protection in a separate study (see below).

The applicant challenged at day 6, which is 5 days after vaccination, long-life broiler chicks from the above study with a vvMDV strain (Md5). These birds were actually vaccinated since the DNA of the 2 vaccine strains was amplified in the spleen of all the tested vaccinates and was not in the spleen of the controls.
None of the vaccinates contracted Marek's disease while 89% of the controls did over the 71 days of monitoring. This study was compliant to Ph. Eur. 0589 requirements, as were the results.

It was concluded that vaccination with a commercial dose was efficacious and met the efficacy requirements from 5 days after vaccination when administered in the field at the hatchery by the SC route to one-day-old commercial long-life broilers.

While a clinical trial performed in pullet chicks has already been assessed for the support of other authorised vaccines, there were groups which are relevant for the efficacy of Prevexxion RN+HVT. Pullet chicks were vaccinated subcutaneously with RN1250 + Cryomarex HVT (similar to Prevexxion RN+HVT) or a commercial Rispens+HVT vaccine at one day of age. From 18 weeks of age onwards, birds were transferred to a laying farm until slaughtering. They were monitored up to 77 weeks of age. The safety results are addressed in the safety part of this report.
The vaccination was effective since the RN1250 vaccine strain was found in 73% of the chickens.
No outbreak of clinical Marek's disease was detected. Anticipating an absence of MDV circulation vaccinates and controls randomly chosen at D1 were challenged in an experimental setting (see thereafter).

Vaccinates and controls from the above study were challenged at day 6 after hatching, which is 5 days after vaccination, with a very virulent MDV strain (RB1B). The design of this study was compliant to Ph. Eur. 0589 and layer chickens were clinically monitored over a 70-day period.
All the controls besides 3 got Marek's disease (25 deaths and 7 surviving birds with Marek lesions) and all the vaccinates were protected. Prevexxion RN+HVT met Ph. Eur. 0589 requirements in term of efficacy.

It was concluded that vaccination with a commercial dose was efficacious and met the efficacy requirements from 5 days after vaccination when administered in the field at the hatchery by the SC route to one-day-old commercial layer pullets.

The proposed claim "to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus)" can be supported based on the results of the presented clinical studies.

Overall conclusion on efficacy

The applicant adequately demonstrated the efficacy of the vaccine.

The results from 2 preclinical and 2 clinical studies show that the product is effective for the active immunisation of one-day-old chickens by the SC route to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus) at the proposed dose of ≥ 2.9 $\log_{10}$ PFU/dose for RN1250 and ≥ 3.0 $\log_{10}$ PFU/dose for HVT FC126.

Onset of immunity

Onset of immunity has been demonstrated at 5 days after vaccination.

Based on the results of the presented study, the proposed claims to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus) are supported.

Duration of immunity

A life long duration of immunity has been justified.

Maternally derived antibodies (MDA)

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

Based on the results of the presented study, the proposed claims to prevent mortality and reduce clinical signs and lesions caused by MD virus (including very virulent MD virus) are supported.

Interactions

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

Clinical trials

In the two clinical studies in long life broilers and in laying hens no MD disease outbreak was reported; however, Ph. Eur. 0589 compliant challenge in subsets of birds have corroborated the efficacy of the vaccine for both types of rearing.

Part 5 – Benefit-risk assessment

Introduction

Prevexxion RN+HVT is a bivalent vaccine intended to be used subcutaneously in one-day-old chickens. The active substances are already authorised cell-associated live virus strains, an engineered Marek's disease virus (MDV-1) serotype 1, named RN1250 strain, in combination with a serotype 3 or turkey herpesvirus (HVT), named HVT FC126. Each 0.2 ml dose of Prevexxion RN+HVT contains 2.9 to 3.9 $\log_{10}$ PFU of serotype 1, strain RN1250 and 3.0 to 4.0 $\log_{10}$ PFU of serotype 3, strain HVT FC126.

At the time of submission, the applicant applied for the following indications: for active immunisation of one-day-old chicks to prevent mortality and clinical signs and reduce lesions caused by Marek's disease (MD) virus (including very virulent MD virus).

Onset of immunity: 5 days after vaccination.

Duration of immunity: a single vaccination is sufficient to provide protection for the entire risk period.

The withdrawal period is zero days.

The dossier was submitted in line with requirements of Article 20 of Regulation (EU) 2019/6.

Benefit assessment

Direct benefit

In 2 preclinical and 2 clinical studies, the vaccine was shown to be efficacious for the active immunisation of one-day-old chicks to prevent mortality and reduce lesions and clinical signs caused by Marek's disease (MD) virus (including very virulent MD virus).

An OOI of 5 days was established against MDV infection both in MDA+ & MDA- vaccinates and no data are provided for the DOI. This is acceptable as the MD virus produces a persistent infection providing a lifelong immunity.

Additional benefits

Prevexxion RN+HVT was shown efficacious against very virulent MDV-1.

The vaccine can be applied at an early age of birds (one-day-old) at the hatchery to provide protection against MDV including very virulent MDV strains so outbreaks due to field contamination are reduced.

The vaccine strains were shown to be fully apathogenic to other avian species as well as limiting the risk to the environment.

Risk assessment

Quality:

Information on the composition, development, manufacturing process, tests performed during manufacture and on the finished product, batch-to-batch consistency and stability data have been provided in a satisfactory manner.

Safety:

Risks for the target animal:

The product is generally well tolerated in the target animal. No adverse reactions were observed after administration of Prevexxion RN+HVT.

No dedicated studies were provided for the biology of the 2 vaccine strains, an apathogenic strain (HVT FC126) and a MDV1 vaccine strain because these strains have already been authorised in other vaccines.

Risk for the user:

The user safety for this product is acceptable when used as recommended and taking into account the safety advice and the special precautions for handling nitrogen stored products listed in the SPC and package leaflet.

Risk for the environment:

The product is not expected to pose any risk to the environment when used as recommended.

Risk for the consumer:

The withdrawal period is proposed at zero days. The concentration of residual antibiotic in the final product has been satisfactorily addressed.

Risk management or mitigation measures

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

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:
For active immunisation of one-day-old chicks to prevent mortality and clinical signs and reduce lesions caused by MDV (including very virulent MDV strains).

The presented data supports only a reduction of clinical signs and thus the claim has been adjusted. The product has been shown to be efficacious for the prevention of mortality and reduction of the clinical signs and lesions caused by MDV and the CVMP agreed to the following indication:

For active immunisation of one-day-old chicks to prevent mortality and reduce clinical signs and lesions caused by MDV (including very virulent MDV strains).

Onset of immunity is adequately supported by data. Duration of immunity for MD is accepted to be life-long. The influence of maternal antibodies on the efficacy of the vaccine against MDV was studied and no negative impact of the onset of immunity has been identified.

The formulation and manufacture of Prevexxion RN+HVT is well-described and the specifications set will ensure that a product of consistent quality will be produced.

Prevexxion RN+HVT is well-tolerated by the target animals and presents a low 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 on quality, safety and efficacy presented by the applicant, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Prevexxion RN+HVT is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 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 medicinal product.