



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 May 2024
EMA/256592/2024
Veterinary Medicines Division

Committee for Veterinary Medicinal Products (CVMP)

CVMP assessment report for Nobilis Multiriva RT+IBm+ND+EDS (EMA/V/C/006043/0000)

Vaccine common name: Avian Metapneumovirus, Infectious Bronchitis virus, Newcastle Disease virus and Egg Drop Syndrome virus vaccine, inactivated.

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

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Introduction	4
Vaccine Antigen Master file (VAMF) and vPTMF	4
Part 1 - Administrative particulars.....	5
Summary of the Pharmacovigilance System Master File.....	5
Manufacturing authorisations and inspection status.....	5
Overall conclusions on administrative particulars	5
Part 2 - Quality	6
Quality documentation (physico-chemical, biological, and microbiological information)	6
Qualitative and quantitative composition	6
Container and closure system	6
Product development	6
Description of the manufacturing method	6
Production and control of starting materials	7
Starting materials listed in pharmacopoeias	7
Starting materials not listed in a pharmacopoeia	7
Control tests during the manufacturing process	8
Control tests on the finished product.....	8
Batch-to-batch consistency	8
Stability.....	9
Overall conclusions on quality	9
Part 3 – Safety documentation (safety and residues tests).....	10
General requirements.....	10
Safety documentation	10
Pre-clinical studies.....	10
Safety of the administration of one dose.....	10
Safety of one administration of an overdose.....	10
Safety of the repeated administration of one dose	11
Examination of reproductive performance	11
Examination of immunological functions	11
User safety	11
Study of residues.....	11
MRLs.....	11
Withdrawal period.....	12
Interactions	12
Clinical studies	12
Environmental risk assessment	17
Overall conclusions on the safety documentation	17
Part 4 – Efficacy documentation (pre-clinical studies and clinical trials)...	19
General requirements.....	19
Challenge model.....	19
Efficacy documentation.....	20
Pre-clinical studies	20
Clinical trials	27
Overall conclusion on efficacy.....	31

Part 5 – Benefit-risk assessment 33

Benefit assessment..... 33

Risk assessment..... 33

Risk management or mitigation measures 34

Evaluation of the benefit-risk balance..... 35

Conclusion 35

Introduction

The applicant Intervet International B.V. submitted on 31 January 2023 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Nobilis Multiriva RT+IBm+ND+EDS, 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 15 June 2022 as no other marketing authorisation has been granted for the veterinary medicinal product within the Union.

Nobilis Multiriva RT+IBm+ND+EDS is an emulsion for injection for chickens containing inactivated avian metapneumovirus strain BUT1 #8544, inactivated avian infectious bronchitis virus strain M41, inactivated avian infectious bronchitis virus strain 4/91, inactivated Newcastle disease virus strain Ulster, and inactivated eggdrop syndrome-1976 virus strain BC14, as active substances, and light liquid paraffin as adjuvant.

The vaccine is presented in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses).

The vaccine is to be administered intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

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

For the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus.
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (GI-23 genotype) and Q1 (GI-16 genotype).
- reduction of mortality and clinical signs caused by Newcastle disease virus.
- reduction of egg drop and eggshell defects caused by eggdrop syndrome-1976 virus.

The rapporteur appointed is Jacqueline Poot 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 22 May 2024, the CVMP adopted an opinion and CVMP assessment report.

On 17 July 2024, the European Commission adopted a Commission Decision granting the marketing authorisation for Nobilis Multiriva RT+IBm+ND+EDS.

Vaccine Antigen Master file (VAMF) and vPTMF

VAMFs for Nobilis Multiriva RT+IBm+ND+EDS (EMA/V/C/006043/0000) were assessed and approved in the context of the MAA for the parent product, Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS (EMA/V/C/005887/0000).

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) with 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

Refer to the respective vaccine antigen master files.

Finished product

Merck Sharp Dohme Animal Health S.L., Salamanca, Spain, is performs the manufacturing of the finished product.

A manufacturing authorisation was issued on 24 November 2020 by the competent authority of Spain (AEMPS). A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 16 February 2022, referencing an inspection on 16 December 2021, by the competent authority of Spain (AEMPS).

Intervet International B.V., Wim de Körverstraat 35, 5831AN Boxmeer, the Netherlands, performs batch release. Proof of establishment in the EEA was provided.

A manufacturing authorisation was issued on 19 December 2022 by the Ministry of Agriculture, Nature and Food Quality of the Netherlands. A GMP certificate confirming compliance with the principles of GMP is provided. The certificate was issued on 23 July 2020, referencing an inspection on 16 July 2020, by the Ministry of Agriculture, Nature and Food Quality of the Netherlands.

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

Nobilis Multiriva RT+IBm+ND+EDS is an inactivated viral poultry vaccine presented in bottles containing 300 ml (1000 doses) or 600 ml (2000 doses).

The vaccine consists of the following antigens: inactivated avian metapneumovirus (AMPV) strain BUT1 #8544, inactivated avian infectious bronchitis virus (IB) strain M41, inactivated avian infectious bronchitis (IB) virus strain 4/91, inactivated Newcastle disease (ND) virus strain Ulster and inactivated eggdrop syndrome-1976 virus (EDSV) strain BC14 as active substances and light liquid paraffin as adjuvant. Polysorbate 80, sorbitan oleate and PBS are included as excipients.

Container and closure system

The product is packed in polyethylene terephthalate (PET) containers (compliant with Ph.Eur. 3.2.2, USP 661, USP 87 and USP 88), closed with halogenated butyl rubber stoppers (Ph.Eur. 3.2.9) and aluminium caps. Containers and stoppers are sterilised by ionising radiation at a minimum dose of 25 kGy. Example certificates of analysis for the packaging materials are provided in the dossier.

Product development

The Nobilis Multiriva inactivated vaccine range can be regarded as the successor of the Nobilis inactivated vaccine range containing the inactivated avian metapneumovirus (AMPV), infectious bronchitis virus (IBV), Newcastle disease virus (NDV), infectious bursal disease virus (IBDV), avian reovirus (ARV) and egg drop syndrome virus (EDSV) antigens.

The dose of Nobilis Multiriva vaccine range is 0.3 ml, compared to the vaccine dose of 0.5 ml of the Nobilis inactivated vaccine range manufactured by the applicant.

The AMPV, IBV M41 and EDSV antigens in the Nobilis Multiriva vaccine range are the same as in the Nobilis inactivated vaccine range. The IBV D274 strain present in the Nobilis inactivated vaccine range was replaced in Nobilis Multiriva by the IBV 4/91 strain, which is included to provide a broader protection due to its higher global presence. The NDV Clone 30 strain was replaced by the NDV Ulster strain, which is included to provide a broader protection in combination with live priming with NDV Clone 30. The adjuvant (oil phase of the emulsion) is the same as for the Nobilis inactivated vaccine range.

The control tests were updated replacing animal testing where possible.

Description of the manufacturing method

Manufacturing of the vaccine

Active substances are manufactured as described in the respective vaccine antigen master files. For all antigens standard manufacturing methods are used. Virus strains are cultured mostly on primary chicken cells and are subsequently inactivated and concentrated where appropriate. The processes

were appropriately validated, and control tests are adequate to assure the quality and consistency of the antigens.

The final product is manufactured by adding the inactivated antigen suspensions to PBS solution. Oil-soluble constituents (sorbitan oleate and polysorbate 80) are dissolved in liquid paraffin and the solution is sterilised. The oil solution and the aqueous suspension are subsequently mixed and emulsified. An example formulation calculation is provided.

Bottles are filled and closed with a stopper and secured with a cap. The final product is stored at 2-8 °C.

The process is considered to be a standard manufacturing process for this type of vaccines. The major steps of the manufacturing process have been validated by three consecutive batches. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible and consistent manner. The in-process controls are adequate for this type of manufacturing process.

Production and control of starting materials

Starting materials listed in pharmacopoeias

Starting materials listed in pharmacopoeias and used for manufacturing of antigens are listed in the respective VAMFs. Certificates of analysis have been provided and all conform to the relevant specifications.

Starting materials listed in pharmacopoeias and used in the production of the finished product are:

Disodium phosphate dihydrate	Ph. Eur. Monograph 0602
Paraffin, light liquid	Ph. Eur. Monograph 0240
Polysorbate 80	Ph. Eur. Monograph 0428
Sodium chloride	Ph. Eur. Monograph 0193
Sodium dihydrogen phosphate dihydrate	Ph. Eur. Monograph 0194
Sorbitan oleate	Ph. Eur. Monograph 1041

Example certificates of analysis are provided for these starting materials and all materials comply with Ph. Eur. requirements.

Starting materials not listed in a pharmacopoeia

Starting materials of biological origin

Starting materials of biological origin, not listed in pharmacopoeias and used in the manufacturing of the antigens are listed in the respective VAMFs. The seed materials are sufficiently characterised and appropriate tests have been performed to assure their quality. Other materials of biological origin conform to the in-house specifications as illustrated by certificates of analysis. The materials used conform to the requirements. No other starting materials of biological origin are used in the manufacturing of the finished product.

Starting materials of non-biological origin

Starting materials of non-biological origin, not listed in pharmacopoeias and used in the manufacturing of antigens are listed in the respective VAMFs. These materials are adequately described and of appropriate quality. No other starting materials of non-biological origin are used in the manufacturing of the finished product.

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

Information regarding the qualitative and quantitative composition of culture media used in the manufacturing of the antigens, their treatment processes and their storage conditions is provided in the respective VAMFs. The risk of contamination with extraneous agents was evaluated and considered negligible for each antigen.

Information regarding the qualitative and quantitative composition of solutions used in the manufacturing of the final product, their treatment processes and their storage conditions is provided in the dossier. All components are either tested for or treated to ensure that there are no contaminants.

A TSE risk assessment on the finished product is provided in accordance with EMEA/410/01. The risk that the vaccine transmits TSE to chickens is estimated as practically zero.

Control tests during the manufacturing process

The control tests performed during the manufacture of the antigens are described in the respective VAMFs. These in-process control tests have been appropriately validated and are deemed to be sufficient to control all critical steps in the manufacturing of the antigens.

The only control test performed during the manufacturing of the finished product is filling volume. The relevant test method (weighing) is considered to fall under GMP. This in-process test is deemed to be sufficient to control the critical step in the manufacturing of the finished product.

Control tests on the finished product

A description of the methods used for the control of the finished product (appearance, viscosity, accelerated stability [stability of the emulsion], identity and potency, type of emulsion, free formaldehyde, sterility) and the respective specifications were provided.

The proposed tests are considered adequate to control the quality of the finished product. In general, the tests performed on the finished product were appropriately validated and limits have been set.

Batch-to-batch consistency

The results of in-process and finished product testing on 3 consecutive batches of finished product of the full-range vaccine (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS) and one additional batch of Nobilis Multiriva RT+IBm+ND+Gm+REOm (no EDS antigen) are presented. All batches conformed with all requirements and consistent results were obtained.

Stability

The stability of the bulk antigens is addressed in the respective VAMFs. From the data provided, the antigen's different storage periods have been adequately demonstrated.

The proposed shelf life of the product is 24 months at 2-8 °C. A long-term stability study was performed, including 17 batches of full-range vaccine and 3 fall-out product batches. Batches were tested for appearance, viscosity, sterility (at the end of the storage period, to confirm integrity of closure) and potency all antigens. Stability could be confirmed for at least 27 months of storage thereby supporting the proposed 24 months shelf life. For the AMPV component a confirmatory in vivo test can be performed in order to assure potency in case antigenic mass ELISA values fall below the lower limit toward the end-of-shelf-life.

The data provided in support of a 10-hour in-use shelf life are considered adequate. The emulsion was stable at the higher temperature, as was the potency. The data are considered adequate to cover storage for 10 hours at room temperature.

Overall conclusions on quality

Nobilis Multiriva RT+IBm+ND+EDS is an emulsion for injection for chickens containing inactivated avian metapneumovirus strain BUT1 #8544, inactivated avian infectious bronchitis virus strain M41, inactivated avian infectious bronchitis virus strain 4/91, inactivated Newcastle disease virus strain Ulster and inactivated egg drop syndrome '76 virus strain BC14, as active substances and light liquid paraffin as adjuvant. The vaccine is presented in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses).

The manufacturing method consists of blending of the different components followed by emulsification and can be considered as standard for this type of vaccine. For each of the antigen components a vaccine antigen master file is presented. For all antigens standard manufacturing methods are used. The processes were appropriately validated, control tests are adequate to assure the quality and consistency of the antigens.

Procedures have been implemented to ensure the absence of extraneous agents in the starting materials of animal origin. A TSE risk assessment for the starting materials used is provided. The risk that the final product may transmit TSE to the target animal is considered negligible.

The production method, including appropriate in-process controls and quality controls on the finished product, together with control of the starting materials, generally ensures a consistent quality of batches of vaccine. The whole production process was evaluated at production scale and shown to be consistent.

In general, the data provided support the proposed 24-month shelf life. Stability data of broached product kept at elevated temperatures show that the vaccine remains stable at 37°C for 3 days, so the proposed 10-hour in-use shelf life at room temperature is considered sufficiently supported.

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

Part 3 – Safety documentation (safety and residues tests)

General requirements

The active substances of Nobilis Multiriva RT+IBm+ND+EDS are inactivated avian metapneumovirus, inactivated avian infectious bronchitis virus, inactivated Newcastle disease virus, and egg drop syndrome virus. Liquid paraffin (mineral oil) is included as adjuvant. The vaccine is to be administered to chickens intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

A full safety file in accordance with Article 8(1)(b) of Regulation (EU) 2019/6 has been provided.

Safety documentation

Tests with the full-range vaccine out of the Nobilis Multiriva range (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS) are presented to substantiate the safety of Nobilis Multiriva RT+IBm+ND+EDS. Five safety studies were conducted to investigate the safety of the product and included one pre-clinical study investigating the safety of the administration of one dose and four clinical trials.

Pre-clinical studies

Safety of the administration of one dose

One pivotal GLP safety study was provided. Safety of a single dose and of a double dose of vaccine was studied in 7-week old SPF birds. In order to achieve the 200% antigen content, multiple vaccine blends had to be used (not all components of the full combination can be blended at 200% in one preparation, due to space limitations). Groups of 11 birds received one of the following: a single dose of the complete vaccine (0.3 ml), a double dose of the complete vaccine (0.6 ml), a single dose of a vaccine containing AMPV and EDSV antigens blended at 200% (0.3 ml), a single dose of a vaccine containing IBV, NDV, IBDV and ARV antigens blended at 200% (0.3 ml) or a 1:1 mix of the two 200% antigen vaccines (0.6 ml).

During the 14-day observation period, the birds were examined daily for clinical signs, intercurrent deaths and local reactions. None of the chickens showed abnormal signs of disease or died from causes attributable to vaccination during the observation period. No palpable local reactions were found in any of the birds. Post-mortem macroscopic and microscopic examinations were not performed.

On the basis of the results no safety concerns arose following the administration of the recommended dose or the double dose to chickens slightly below the minimum recommended age, providing therefore a valid demonstration of the safety of a single dose of the product. The absence of post-mortem data is considered justified, based on the high similarity of the composition of the product to the existing inactivated virus vaccines for poultry and the absence of palpable local reactions.

Safety of one administration of an overdose

No overdose studies are required for inactivated vaccines.

Safety of the repeated administration of one dose

The vaccine is to be given once during a lifetime. No repeated dose safety studies are therefore required.

Examination of reproductive performance

The vaccine is not intended for use during lay. As an inactivated vaccine, the product is not considered a risk to the developing reproductive system. No specific studies were performed. During field studies no differences were observed between vaccinated and control birds with respect to laying performance. A warning is included in the SPC to not use the product during lay or within 3 weeks before the onset of lay.

Examination of immunological functions

The product is an inactivated vaccine and none of the components are considered a risk for the immune system, therefore no studies were performed.

User safety

The applicant has presented a user safety risk assessment which has been conducted in accordance with CVMP guideline EMEA/CVMP/IWP/54533/2006 (and EMA/CVMP/543/03-Rev.01).

The main potential routes of accidental contact with the product have been considered and it was concluded that the most likely are those of accidental self-injection and dermal and/or oral exposure.

The active substances are inactivated viruses and not infectious to humans. The excipients, including adjuvants, are commonly used in other vaccines and do not present a safety concern. The light mineral oil included in the formulation is of concern since an accidental self-injection may have consequences that could, in the very worst-case, lead to loss of a digit due to blockage of blood vessels as a result of the pressure caused by inflammatory reactions.

As a result of the user safety assessment adequate information is included in section 3.5 of the SPC and since the product contains mineral oil, the standard warning for mineral oil-containing vaccines is included, appropriately, in the product literature.

Based on the above risk assessment the CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Study of residues

No studies of residues were performed. This is considered acceptable.

MRLs

The active substance, being a principle of biological origin intended to produce active immunity, is not within the scope of Regulation (EC) No 470/2009.

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

The antimicrobial substances used in the manufacturing of the antigens are present at low residual levels in the finished product, which is not considered to constitute a risk to the consumer.

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.'

Clinical studies

Tests with the largest combination of the Nobilis Multiriva vaccine range (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS) with the highest number of different antigens (9) are presented to substantiate the safety and efficacy of Nobilis Multiriva RT+IBm+ND+EDS. Four single-centre, non-randomised, open, positive-controlled, two-armed GCP-compliant clinical studies with matched flocks were conducted to evaluate safety and efficacy in layer and broiler breeders. The studies were conducted in the Netherlands in well-managed farms.

All four studies were well designed and conducted and confirmed that the product is safe in both layer and broiler breeders when applied as part of the standard vaccination program.

Study 1: A field trial in the Netherlands to assess the safety and efficacy of a RT+IBm+ND+Gm+REOm+EDS vaccine in breeders	
Study sites	Broiler breeder farm in the Netherlands, matched houses.
Study design	Open, positive-controlled, two-armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional broiler breeders, originating from the same parent flocks and of the same age, were evenly distributed over the houses to obtain identical flocks of approximately 18,000 birds.
Test product	Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac. 0.5 ml i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 14 th week of life (right side breast muscle) while birds in the control group were vaccinated with the two control vaccines (in right and left side breast muscle). Prior to and after the 14 th week, both flocks received all standard vaccinations for the farm.

Safety end-points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production and hatchability was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication were recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake were scored as normal on all observation days. A local reaction was observed in one bird (out of 15 tested) of the control group on day 7. In the test group on day 4, one bird showed a 2 cm long subcutaneous haemorrhage in the right breast, likely a result of mechanical trauma. On day 14 one bird had a large (10 x 3.5) subcutaneous reaction in the right breast. This concerned a hard swelling showing signs of inflammation (swollen and red). The bird was in good general condition. An additional scoring on day 20 revealed no further local reactions. The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was good and highly comparable between groups. Fluctuations were due to general causes and detectable in both groups. Hatchability was highly similar.
Adverse events	Local reactions were observed both in the test and control groups.
Discussion	
Discussion/conclusions further to assessment	<i>The study was appropriately designed and conducted to an acceptable standard (GCP). While some local reactions were observed in the test group (but also in the control group), this did not lead to any changes in the performance of the flock when compared to the positive control group.</i> <i>The study is considered to support the safety of the vaccine when applied under field conditions.</i>

Study 2, A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in layers	
Study sites	Layer farm in the Netherlands, matched houses.
Study design	Open, positive-controlled, two-armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional layers, originating from the same parent flocks and of

	the same age, were evenly distributed to obtain identical groups. Groups were housed in different rows of the rearing house and later placed in two houses to obtain identical flocks of approximately 10,000 birds.
Test product	Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 12 th week of life (right side breast muscle) while birds in the control group were vaccinated with the control vaccine (right side breast muscle). Nobilis Salenvac T was applied at the same time as the study products, in the left breast muscle. Prior to and after the 12 th week, both flocks received all standard vaccinations for the farm.
Safety end-points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication were recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake were scored as normal on all observation days. Local reactions were not observed in control or test group. The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was comparable between groups.
Adverse events	No immediate or local reactions observed.
Discussion	
Discussion/conclusions further to assessment	<i>The study was appropriately designed and conducted to an acceptable standard (GCP). No general or local reactions were observed, and performance of the test and control groups was highly similar and within normal ranges. The study is considered to support the safety of the vaccine when applied in layers under field conditions.</i>

Study 3, A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in layers

Study sites	Layer farm in the Netherlands, matched houses.
Study design	Open, positive-controlled, two-armed (matched flocks).

Compliance with regulatory guidelines	GCP compliant
Animals	Conventional layers, originating from the same parent flocks and of the same age, were evenly distributed to obtain identical groups. Groups were housed in different rows of the rearing house and later placed in two houses to obtain identical flocks of approximately 12,500 birds.
Test product	Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis RT+IBmulti+G+ND 0.5 ml, i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 12th week of life (right side breast muscle) while birds in the control group were vaccinated with the two control vaccines (in right and left side breast muscle). Avian encephalomyelitis/fowl pox vaccine was applied via wing web and Nobilis ILT via ocular route as the same time as the test and control vaccines. Prior to and after the 12th week, both flocks received all standard vaccinations for the farm.
Safety end/points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication were recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	General health and feed intake were scored as normal on all observation days. Local reactions were not observed in the test or control groups. Mortality was similar in both groups and somewhat higher than normal, which was attributed to feather pecking. Egg production was within normal ranges and comparable between groups.
Adverse events	Immediate or local reactions were not observed.
Discussion	
Discussion/conclusions further to assessment	<i>The study was appropriately designed and conducted to an acceptable standard (GCP). No general or local reactions were observed, and performance of the test and control groups was highly similar and within normal ranges. The study is considered to support the safety of the vaccine when applied in layers under field conditions.</i>

Study 4, A field trial in the Netherlands to assess the safety and efficacy of the RT+IBm+ND+Gm+REOm+EDS vaccine in broiler breeders primed with REOm	
Study sites	Broiler breeder farm in the Netherlands, matched houses.
Study design	Open, positive-controlled, two-armed (matched flocks).
Compliance with regulatory guidelines	GCP compliant
Animals	Conventional broiler breeders, originating from the same parent flocks and of the same age, were evenly distributed over the houses to obtain identical flocks of approximately 12,000 birds.
Test product	Nobilis Multiriva REOm 0.3 ml, i.m. Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, 0.3 ml, i.m.
Control product/ Placebo	Nobilis REO 1133 (0.2 ml) plus Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac. 0.5 ml, i.m.
Vaccination scheme	Birds in the test group were vaccinated with the test product in the 8th week of life (Nobilis Multiriva REOm) and 12th week of life (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS). Birds in the control group were vaccinated in the 8th week of life with Nobilis REO 1133 and in the 12th week with Nobilis RT+IBmulti+G+ND 0.5 ml, i.m. plus Nobilis Reo inac.. Concurrent with the vaccination at 8 weeks of age, birds were vaccinated via wingweb with Tremvac. Prior to and after these vaccinations, both flocks received all standard vaccinations for the farm.
Safety end-points	Daily general health and feed intake for 2 weeks post vaccination (p.v.). Local reactions scored on 15 randomly selected birds in each group on days 1, 4, 7 and 14 p.v. and weekly thereafter until resolved. Egg production and hatchability was monitored for each group throughout the period of lay. Throughout the study, daily mortality, vaccinations and the use of medication was recorded.
Statistical method	Descriptive statistics (two groups)
Results	
Outcomes-Safety observations	Some data could not be collected as planned due to COVID-19 restrictions (hatchability data). General health and feed intake was scored as normal on all observation days. A local reaction was observed in one bird (out of 15 tested) in the test group on day 7 (subcutaneous haemorrhage, Nobilis Multiriva REOm) and in one bird on Day 15 (hard nodule in right breast 3x1 cm, Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccination), the birds looked otherwise healthy. No local reactions were found one week later. Local reactions were found in one bird of the control

	group on Day 15 (mild subcutaneous inflammation in the right breast: Nobilis RT+IBmulti+G+ND vaccination. The mortality numbers were similar in both groups and comparable to normal mortality figures for this type of bird. Egg production was good and highly comparable between groups. Hatchability was tested once and was similar.
Adverse events	Local reactions were observed both in the test and control groups.
Discussion	
Discussion/conclusions further to assessment	<i>The study was appropriately designed and conducted to an acceptable standard (GCP). While some local reactions were observed in the test group (but also in the control group), this did not lead to any changes in the performance of the flock when compared to the positive control group.</i> <i>The study is considered to support the safety of the vaccine when applied to broiler breeders under field conditions.</i>

Environmental risk assessment

An environmental risk assessment has been performed in accordance with EMA Note for guidance on environmental risk assessment for immunological veterinary medicinal products (EMA/CVMP/074/95-Final). The assessment can stop in phase one.

The product is a vaccine containing inactivated viral poultry antigens and is adjuvanted with light liquid paraffin. Polysorbate 80, sorbitan oleate and PBS are included as excipients. The product is used in chickens and is administered intramuscularly. Therefore, direct exposure of the environment to the product does not take place. Any unused product or waste material does not pose an environmental risk. The product and waste should nevertheless be disposed by the appropriate channels, and adequate advice is given in the product literature. As no live micro-organisms are present in the product, hazards and risks from the active ingredients are considered negligible. Excretion of any of the active compounds of the product or their metabolites by vaccinated animals, if occurring at all, will only be in minute amounts and does not pose a risk to the environment. In conclusion, this veterinary medicinal product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

By testing the largest combination of the Nobilis Multiriva vaccine range (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS) with the highest number of different antigens (9), the data found in the safety studies are considered applicable to Nobilis Multiriva RT+IBm+ND+EDS.

The safety of a standard dose and a double dose of the vaccine was tested in a GLP study. The vaccine is blended to contain a standard dose of each antigen and thus there are no minimum or maximum potency vaccine batches. From the results it can be concluded that the vaccine is safe in birds from 7 weeks of age, when applied in accordance with the SPC.

The vaccine is to be applied once during the production lifetime of the birds. No repeated dose safety studies are therefore required.

The vaccine is not intended for use during lay. As an inactivated vaccine, the product is not considered a risk to the developing reproductive system. No specific studies were performed, and this is acceptable. A warning is included in the SPC to not use the product during lay or within 3 weeks before the onset of lay.

The product is an inactivated vaccine and none of the components are considered a risk for the immune system, therefore no studies were performed. The absence of specific studies or data on immunological functions is adequately justified.

The results of four field safety and efficacy field trials indicated no safety issues. The data are considered to support the safety of the vaccine when used in field conditions. In the field trials, no differences were observed between vaccinated and control birds with respect to laying performance, supporting the notion that the product does not pose a risk to the developing reproductive system when used as recommended.

A comprehensive user safety assessment has been provided by the applicant. Mineral oil was pointed out as the major concern. The standard warning for mineral oil-containing vaccines is used, which is considered appropriate. The user safety has been adequately addressed and appropriate warnings are included in the SPC.

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

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

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

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

General requirements

Nobilis Multiriva RT+IBm+ND+EDS is to be administered to chickens intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay.

The applicant applied for the following indications:

For the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus.
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (GI-23 genotype) and Q1 (GI-16 genotype).
- reduction of mortality and clinical signs caused by Newcastle disease virus.
- reduction of egg drop and eggshell defects caused by egg drop syndrome '76 virus.

The onset of immunity is 4 weeks post-vaccination, and a duration of immunity is 100 weeks of age for AMPV, IBV, NDV, and EDSV.

The vaccine is positioned for use in chickens that have received primary vaccinations with live or inactivated vaccines against infectious bronchitis virus (e.g. Nobilis IB 4/91, Nobilis IB Ma5). This requirement is included in the SPC section 3.9. Therefore, data derived from studies in chickens that had received such prime-boost vaccinations were used for IBV to support onset and duration of efficacy. For AMPV, NDV and EDSV efficacy was determined in studies in non-primed birds, receiving only vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS.

Challenge model

The application of the AMPV-B 11/94 strain via the intravenous route did induce clinical signs of AMPV and the use of this challenge strain is considered sufficiently justified. There are several studies in public literature on avian and human metapneumoviruses which conclude that there is a relation between protection and antibody responses to the fusion protein (F-protein). Therefore, it can be accepted that antibody titres against F-protein are used as an indicator of immunity.

In order to demonstrate a broad protection against all genotype-I IBV strains, the following challenge strains were used: M41 (GI-1), 4/91 (GI-13), QX (GI-19), Var2 (GI-23) and Q1 (GI-16). These challenge strains cover the different viral lineages within the genotype I-cluster. Vaccination challenge studies were set up in accordance with the Ph. Eur. monographs 0959 and 5.2.7. Both the ocular and intratracheal routes of challenge were used to induce drop in egg production and eggshell defects. As IBV-specific antibodies are related to protection, serological analysis (HI assay) was performed in pre-clinical and clinical studies.

Efficacy studies for NDV were set up in accordance with Ph. Eur. 0870 and 5.2.7, using the Herts 33/56 challenge strain. As NDV-specific antibodies are related to protection, serological analysis (HI assay) was performed in vaccinated animals in both pre-clinical and clinical studies.

For EDS, vaccination challenge studies were set up in accordance with Ph. Eur. 5.2.7 and 1202 and

using the EDSV M13 challenge strain. The main clinical parameter assessed was the percentage of egg drop and eggshell defects. Serological analysis (HI assay) was performed in vaccinated animals in both pre-clinical and clinical studies.

Efficacy documentation

Tests with the full range vaccine (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS) are presented to substantiate the efficacy of Nobilis Multiriva RT+IBm+ND+EDS. A total of 40 studies were conducted to investigate the efficacy of the product and included 27 pre-clinical studies and 4 clinical trials that were further analysed in 9 separately reported serological and challenge studies. Laboratory studies were well documented and carried out in chickens of the minimum age recommended for vaccination, using pilot batches. Pilot batches were also used in the clinical trials.

Pre-clinical studies

Dose determination

Since the Nobilis Multiriva RT+IBm+ND+EDS can be considered as an update and extension of the existing range of Nobilis inactivated vaccines, the dose has been established based on prior experience.

Onset of immunity

AMPV

In one study, serological responses to IBV and AMPV after vaccination were analysed. Day-old SPF laying hens were divided into 4 groups of 20 birds. One group was left untreated (control), one group was vaccinated at Day 0 with live AMPV vaccine (Nobilis Rhino CV) and at 15 weeks with the test vaccine ("AMPV live"), one group was vaccinated at Day 0 with live IB vaccines (Nobilis IB Ma5 and 4/91) and at 15 weeks with the test vaccine ("IBV live"), and one group was vaccinated with the test vaccine at 15 weeks (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS).

Blood samples were taken regularly from all treatment groups up to 99 weeks of age. AMPV antibody responses were analysed in a competitive ELISA using vaccine antigen. No AMPV-specific antibodies were detected after live AMPV vaccination (priming). Five weeks after vaccination with the test vaccine, AMPV antibodies were detected in vaccinates, with average titres in the "AMPV live" group much higher ($6 \log_2$ U/ml) compared to the (non-primed) "IBV live" and test vaccine groups ($3.5-4 \log_2$ U/ml). In all vaccinated groups, titres persisted until 99 weeks of age with a slight decline. The control group remained negative throughout ($3 \log_2$ U/ml).

The study was appropriately designed and executed to an acceptable standard. The study can be considered valid since controls remained AMPV seronegative. It can be concluded that (both with and without priming) antibodies against AMPV appeared 5 weeks after vaccination (first sampling) and persisted for up to 84 weeks after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS.

Two challenge studies were performed, at 26 and 60 weeks of age, however the challenge was too weak, and no conclusions could be drawn. The decision not to repeat the studies and proceed with the results of study 2 only (DOI, challenge at 95 weeks of age) can be supported based on 3Rs considerations. The vaccine was shown to provide protection at 80 weeks post vaccination. Average

antibody titres $\geq 3.6 \log_2$ can be considered related to protection, and serology can be used to support onset and duration of immunity. An additional serological study was performed in SPF birds vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age and samples taken at 20 weeks of age. The average antibody titre at 4 weeks post vaccination was $3.2 \log_2$ and thus lower than the minimum level associated with protection.

In conclusion, the claimed onset of immunity of 4 weeks for the AMPV component is not sufficiently supported by data. A protective serological response after vaccination (non-primed) was first detected at 5 weeks post vaccination and there are no data to support that responses prior to this timepoint would be adequate to reduce clinical signs of AMPV infection. The OOI for AMPV, as stated in the product information, is 5 weeks.

IBV

Serological responses to IBV and AMPV after vaccination were analysed in the same study described above for AMPV. Day-old SPF hens were divided into 4 groups of 20 birds. One group was left untreated (control), one group was vaccinated at Day 0 with live AMPV vaccine (Nobilis Rhino CV) and at 15 weeks with the test vaccine ("AMPV live"), one group was vaccinated at Day 0 with live IB vaccines (Nobilis IB Ma5 and 4/91) and at 15 weeks with the test vaccine ("IBV live"), and one group was vaccinated with the test vaccine at 15 weeks (Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS).

Blood samples were taken regularly from all treatment groups up to 99 weeks of age. Antibodies to IBV M41 and IBV 4/91 were determined by HI test. Overall, similar serological profiles for both anti-IBV M41 and anti-IBV 4-91 antibodies were observed for each individual treatment group, albeit the average titres were higher for IBV 4-91 antigen. From 20 weeks of age, birds in the non-vaccinated treatment group showed levels of non-specific reactivity for both anti-IBV M41 antibodies and anti-IB 4-91 antibodies, typical of the age of the birds ($\leq 5 \log_2$). Priming with live Nobilis IBV vaccines induced an initial IBV antibody response peaking around 8 to 12 weeks of age at around $7-8 \log_2$. Following boosting with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, the antibody levels increased to around $11 \log_2$ and these levels persisted with a slight decline to at least 90 weeks of age. Non-IBV-primed birds showed a clear response following administration of the inactivated vaccine, but the titres achieved were lower than in the IBV-primed birds ($8-9 \log_2$). At the 99-week timepoint, titres had increased in all groups except the "IBV live" group. This was likely an effect of IBV exposure; so no conclusions can be drawn after week 90. It can be concluded that an antibody response was detectable from 5 weeks until 75 weeks post vaccination.

In another study, birds in group 2 were vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age. At 4 weeks post vaccination the M41 HI titre in this group was on average 7.7 and the 4/91 HI titre was 8.2. These titres at 4 weeks p.v. were not significantly different from those measured at 5 weeks post vaccination in the previous. These data support an onset of immunity of 4 weeks for IBV.

Several studies were performed to assess the protection of Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS against IBV challenge. In the first study, four groups of 40 day-old SPF birds were included. One group was left untreated (control), one group was vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks of age, one group was vaccinated at day of age with live IB Ma5 and at 15 weeks with the test vaccine (prime-boost) and one group was vaccinated with live IB Ma5 at day of age (live IB). At 15 weeks of age each group was divided into 4 pens; egg production and quality were recorded per pen. At 26 weeks of age, the birds were challenged with IBV M41 via ocular route and monitored for 4 weeks. In the controls, the maximum egg drop was 18.6%, which is below the requirements for a valid test in Ph. Eur. 0959 (35%). The average post-challenge egg production in the vaccinated groups was higher by 10% (test vaccine),

12% (live IB) or 13% (prime-boost) compared to the controls. The study met the requirements of the OIE terrestrial manual for egg-drop in the controls (>15%) and the vaccinated (prime-boost) group experienced no drop in egg production, indicating complete protection. In other studies, with challenges at later stages after vaccination, a more pronounced drop in egg production was achieved in controls while again vaccinates were protected. It is agreed that in the interest of 3Rs, it is not desirable to repeat the study for protection at peak of lay.

The set-up of the second study was similar to the previous one, however the birds were challenged with IBV 4/91 strain. Egg drop in the controls was 5% at 2 weeks post challenge; the study was considered invalid.

The third included 4 groups of 55 day-old SPF birds. One group was left untreated (control), one group was vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, one group was vaccinated at day of age with live IB 4/91 and at 16 weeks with the test vaccine (prime-boost) and one group was vaccinated with live IB 4/91 at day of age (live IB). At 18 weeks of age, 48 animals in each group were divided into 4 pens per group; egg production and quality were recorded per pen. At 27 weeks of age, the birds were challenged with IBV 4/91 via intratracheal route and monitored for 4 weeks. The challenge did not result in a strong effect on average egg production (-13.8% in controls) and is not valid in accordance with Ph. Eur. 0959 requirements (at least 15% reduction). Moreover, it is noted that the vaccinated group with the lowest antibody response (live IB) had no drop in egg production whereas test vaccine and prime-boost groups did show a reduction in egg production that was small (5%) but statistically significant. It can be agreed that the reductions in the vaccinated groups after challenge are small and may not be biologically significant. Taken together, these data give only very limited support for the test vaccine efficacy against IBV 4/91 challenge at peak of lay (11 weeks post vaccination). However, at 45 and 81 weeks post vaccination, full protection against drop in egg production due to IBV 4/91 challenge was found in birds that were primed with live IB vaccines and boosted with Multiriva RT+IBm+ND+Gm+REOm+EDS. This is considered adequate to support efficacy against IBV 4/91.

A different study was performed where birds were primed with live IB vaccines (Nobilis IB Ma5 and Nobilis IB 4/91) at day of age, and boosted with Multiriva RT+IBm+ND+Gm+REOm+EDS at 15 weeks. At 25 weeks post vaccination birds were challenged with IB-QX. Controls exhibited a clear drop in egg production which was prevented in the vaccinates. Another study had the same study design but the challenge was performed with IB variant 2. Again, controls exhibited a clear drop in egg production which was prevented in the vaccinates. Finally, the applicant provided a new study in which birds that had received a priming and booster vaccination were challenged at 11 w.p.v. with IB Q1. Full protection against egg-drop was observed in the vaccinates.

The clinical data recorded in the IB vaccination-challenge studies were summarised. From this data, it can be concluded that vaccination with a prime-boost scheme resulted in a reduction of coughing after challenge with IB strains. Thus, protection against respiratory signs caused by IB M41, IB 4-91, IB QX and IB Var2 can be considered adequately supported by data.

In conclusion, taking into account the positioning of the vaccine as a booster after live IB-vaccine priming, the claimed onset of immunity against IBV of 4 weeks is sufficiently supported by data. The serological response after the test vaccine vaccination (non-primed) was first detected at 4 weeks post vaccination and data supporting protection from egg drop at peak of lay are available for IBV M41, QX, Q1 and Var2 types.

NDV

In the first study, serological responses to NDV were evaluated. Seven groups of 34 to 38 day-old SPF chicks were included in the study: one group remained unvaccinated, two groups were vaccinated at day of age with Nobilis ND C2, two groups were vaccinated at day of age with Nobilis ND Clone 30, two groups were not vaccinated at Day 0. At 12 weeks of age, all vaccinated groups received Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS. Blood samples from 15 birds per group were collected at regular intervals. Antibody responses were evaluated by HI test using NDV La Sota and NDV Ulster antigens. Titres in the non-vaccinated controls remained at baseline levels throughout the study. No titres were observed in the non-primed birds prior to vaccination. Priming with live Nobilis ND vaccines induced an initial low anti-ND antibody response. Following boosting with inactivated vaccine, the antibody levels strongly increased, and these levels slowly declined by 30 weeks of age and remained stable up to 100 weeks of age. Titres after single vaccination were lower but clearly detectable from 4 weeks post-vaccination (p.v.) and decreased somewhat by 30 weeks of age to remain stable until 100 weeks of age. The study was appropriately designed and executed, and the results support an onset of immunity of 4 weeks post vaccination and a duration of immunity of 100 weeks of age (88 weeks post vaccination).

The second study was designed fully in accordance with the Ph. Eur. 0870 test for immunogenicity. Three batches of Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS were included in the test: blended at 100%, 75% and 50% of the target NDV antigen quantity. For all three vaccine batches, three dilutions (1/30th, 1/50th and 1/120th dose) were tested for protection against NDV Herts 33/56 challenge. The test can be considered valid since all control birds died within 6 days of challenge. The vaccine complied with the test since the smallest dose (minimum antigen content = 100% batch) corresponded to no less than 50 protective dose 50% (PD₅₀) and the lower confidence limit is no less than 35 PD₅₀. The batches blended at 75% and 50% NDV antigen also complied with the test requirement.

In the third study, a total of 105 day-old SPF birds were included, divided into 7 groups. The groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 16 weeks of age with NDV Herts 33/56 and the birds were monitored for 21 days for clinical signs. All control birds were euthanised within 4 days after challenge due to signs of NDV infection. The results support an onset of immunity of 4 weeks, with 93.3%-100% protection against clinical signs and mortality after vaccination with Nobilis Multiriva RT+IBm+ND+EDS+Gm+REOm with or without priming with Nobilis ND C2 or Nobilis ND Clone 30.

In conclusion, the claimed onset of immunity (reduction of mortality and clinical signs) against NDV of 4 weeks is considered sufficiently supported by the data provided.

EDSV

Study 1 included a total of 216 three-week-old SPF hens assigned to two equally sized groups: group 1 was vaccinated at 16 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccine. Group 2 served as non-vaccinated controls. At 16, 20, 30, 40, 50, 60, 70, 80 and 90 weeks of age, blood samples were collected from 20 chickens from each group. Sera were analysed using an EDSV HI assay. From 21 weeks of age to 90 weeks, egg production and quality were monitored daily. Titres in the non-vaccinated birds remained below the detection level of 4 log₂ throughout the study. Group 1 seroconverted to give a mean titre of 7.7 log₂ four weeks post-vaccination. Mean titres declined slowly to approximately 7.0 log₂ by 50 weeks of age and were then maintained at this level until the end of the study at 90 weeks of age (74 weeks post vaccination). Egg production was consistent and comparable between groups.

In study 2, two groups of 35 SPF hens were included. Group 1 was vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, group 2 remained as non-vaccinated controls. After challenge at 30 weeks of age, the reduction in egg production in group 2 was not statistically significant, nor was the difference between the groups. No conclusions could be drawn.

In study 3, two groups of 36 day-old SPF hens were included. Group 1 was vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at 16 weeks of age, group 2 remained unvaccinated. At 21 weeks of age, hens were housed in 3 pens of 10 animals per group. Egg production and quality was monitored daily from 19 to 36 weeks of age. Challenge was performed at 30 weeks of age. Blood samples were taken at 16, 20, 30 and 36 weeks. Titres in controls remained below detection levels up to week 30. In vaccinates average titres of 5.4 log₂ and 5.2 log₂ were found at 20 and 30 weeks of age, respectively. In the control group egg production was reduced significantly compared to pre-challenge baseline. On average, egg production in the vaccinated group was 50% higher than in the non-vaccinated control group. The percentage of abnormal eggs was low in both groups before and after challenge (<0.6%). The data support the presence of protective immunity at the peak of lay, 14 weeks after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS.

In conclusion, while there is no direct evidence for the claimed onset of immunity of 4 weeks post vaccination for EDSV, based on the serological response observed it can be accepted that a response to vaccination has developed by 4 weeks post vaccination that is likely to confer protection. At 4 weeks p.v. the average antibody response was highest. The first timepoint that challenge was performed, and protection was shown was at peak of lay (14 weeks post vaccination), which is acceptable.

Duration of Immunity

AMPV

In study 1, serological responses to AMPV after vaccination were analysed up to 99 weeks of age (please refer to OOI, above). A serological response after vaccination with the test vaccine (non-primed) was observed until 84 weeks post vaccination.

In study 2, efficacy against AMPV challenge at 95 weeks of age was evaluated. Three groups of 30 day-old SPF layers were included in the study. One group remained untreated (control), one was vaccinated with live AMPV (Nobilis Rhino CV) at day old and with the test vaccine at 15 weeks of age, and one group was vaccinated at 15 weeks of age with the test vaccine. At 92 weeks of age, each group was divided into three pens (10 animals/pen) and egg production (and quality) was monitored daily. The daily mean for the number of eggs produced per day per hen was calculated for each treatment group from 92 weeks until the end of the study. At 95 weeks of age, a challenge was performed with AMPV. There was no serological evidence of previous exposure to AMPV. Upon challenge, the control birds exhibited a significant decrease in egg production and an increase in abnormal eggs count was observed. The challenge can be considered as valid. None of the vaccinated groups showed any sign of egg production loss or reduced egg quality after challenge. It can be concluded that vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS either with or without prior priming with Nobilis Rhino CV protects birds against egg drop caused by AMPV up to 80 weeks post vaccination.

In conclusion, a serological response after vaccination with the test vaccine (non-primed) was observed until 84 weeks post vaccination and birds were shown to be protected from challenge until 80 weeks post vaccination. The claimed DOI of 80 weeks post vaccination for AMPV is therefore supported.

IBV

Serological responses to IBV and AMPV after vaccination were analysed (see OOI above). It can be concluded that an antibody response against IBV M41 and 4/91 was detectable at least until 75 weeks after vaccination (last reliable sample).

Seven studies were performed in which birds were vaccinated against IB using a priming vaccination with IBV live vaccine(s) and a booster vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, and subsequently challenged with IBV.

In the first study, two groups of 20 day-old SPF hens were included. One group remained unvaccinated (control), the other was vaccinated at day of age with live IB Ma5 and IB 4-91 vaccines and at 15 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS. At 57 weeks of age each group was divided over three pens and egg production and quality were monitored. Challenge with IBV M41 was performed at 60 weeks of age and birds were monitored for 4 weeks. In the control group reductions in egg production up to 60.5% were observed. In the vaccinated group there was minimal effect of challenge (6.6% reduction). The study provides support for a duration of immunity of 45 weeks post vaccination in birds primed with live IB Ma5 and IB 4-91 vaccine and vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS against virulent challenge with IBV Massachusetts M41 strain.

Study 2 was set up identically to the study described above, but with challenge at 96 weeks of age. A significant reduction in egg production was observed in the control group (up to 50%) while in the vaccinated group a smaller effect (13%) was observed at 2 weeks post challenge. The study provides support for a duration of immunity of 81 weeks post vaccination in birds primed with live IBV Ma5 and IB 4-91 vaccine and vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, against virulent challenge with IBV Massachusetts M41 strain.

Study 3 was set up identically to study 1, with the exception of the challenge that was performed (at 60 weeks of age) with IBV 4-91 strain. In the control group egg production decreased (up to 24% decrease) in the first two weeks after challenge. In the vaccinated group, egg production remained at pre-challenge level. The study provides support for a duration of immunity of 45 weeks post vaccination in birds primed with live IBV Ma5 and IBV 4-91 vaccine and vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS against challenge with variant IBV 4-91 strain.

Study 4 was set up identically to the study 3 described above, but with challenge at 96 weeks of age. A significant reduction in egg production was observed in the control group (up to 42%), while in the vaccinated group egg production remained at pre-challenge level. The study provides support for a duration of immunity of 81 weeks post vaccination in birds primed with live IBV Ma5 and IBV 4-91 vaccine and vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, against challenge with variant IBV 4-91 strain.

In study 5 two groups of 30 day-old SPF hens were included. One group remained unvaccinated (control), the other was vaccinated at day of age with Nobilis IB Ma5 and Nobilis IB4-91 vaccines and at 15 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS. At 33 weeks of age each group was divided over three pens and egg production and quality were monitored. Challenge with IBV QX strain was performed at 40 weeks of age and birds were monitored for 4 weeks. In the control group, reductions in egg production up to 50.6% were observed. In the vaccinated group there was some effect of challenge (9.3% reduction). The study provides support for protection against egg drop caused by IBV QX strain at 25 weeks post vaccination (40 weeks of age) in birds vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, when primed with live IBV vaccines at one day of age.

Study 6 was designed identically to study 5 described above, but for the challenge performed with Q1 strain. No effect of challenge was observed in either of the two groups and the study was considered invalid.

Study 7 was designed identically to study 5 (described above), except for the challenge strain used: IBV variant 2. Control birds exhibited significant reductions in egg production following challenge (max. 36.1%). In the vaccinated birds, mean weekly egg production was slightly reduced (< 10% of baseline). After challenge, the level of abnormal eggs was higher in the vaccinated group (8.5%) than in the control group (3.9%). The effect on the egg production was re-evaluated by subtracting the abnormal eggs. The evaluation showed that the overall egg production using only well-formed eggs in the four-week period after challenge was significantly higher in the vaccinated birds compared to the non-vaccinated birds. The results are considered to support protection against egg drop caused by IBV variant 2 strain at 25 weeks post vaccination in birds vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, when primed with live IBV vaccines at one day of age.

Finally, the applicant provided a study in which birds that had received a priming and booster vaccination were challenged at 11 w.p.v. with IB Q1. Full protection against egg-drop was observed in the vaccinates.

In conclusion, the serological response to IBV M41 and 4-91 antigens could be reliably detected until 75 weeks post vaccination (non-primed). Challenge data have been provided that support protection after prime-boost schedule (live IBV vaccines followed by Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS). These data support efficacy against M41 and 4/91 challenge at up to 81 weeks post vaccination. Together the data are considered to support the claimed DOI for IBV of 80 weeks post vaccination.

In addition, efficacy of the prime-boost regimen against QX and Var2 challenge at 25 weeks, or against Q1 challenge at 11 weeks post vaccination was shown. Since it is accepted that antibodies are a correlate of protection for IBV, the serological OOI and DOI as determined for M41 and 4-91 strains is also valid for the variant strains that depend on cross reactivity of the antibodies generated against M41 and 4-91 antigens in the vaccine. A claim for cross-protection against QX, Var2 and Q1, separately included in the SPC, is therefore accepted.

NDV

The serological study (described above for OOI) provides support for an immune response that is maintained at a stable level until 100 weeks of age (88 weeks post vaccination).

Study 1 included a total of 126 day-old SPF chicks divided into 7 groups. Groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 60 weeks of age with NDV Herts 33/56, and birds were monitored for 21 days for clinical signs. Twelve out of thirteen control birds died of NDV. The vaccinated groups were significantly protected (80-100%). The results support a duration of immunity of 48 weeks, with protection against clinical signs and mortality after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS with or without prior priming with Nobilis ND C2 or Nobilis ND Clone 30.

In studies 2 and 3, the efficacy of the NDV component at 100 weeks of age was tested. A total of 126 day-old SPF chicks were divided into 6 groups. Groups were either not vaccinated (control), vaccinated at 12 weeks of age with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, primed with Nobilis ND C2 and boosted with the test vaccine or primed with Nobilis ND Clone 30 and boosted with the test vaccine. All groups were challenged at 100 weeks of age with NDV Herts 33/56, and birds were monitored for 21 days for clinical signs. All controls died or were euthanised due to severe signs within 3 days. All vaccination regimes provided significant protection ($P < 0.0001$) against NDV challenge at 100 weeks of age ranging from 80% to 93% protection from clinical signs and mortality.

In conclusion, the claimed DOI of 80 weeks post vaccination is considered sufficiently supported by data. Challenge at 88 weeks post vaccination showed significant protection, and serology indicates a stable response up to this date.

EDSV

As observed in study 1 (refer to section on OOI for EDSV), a stable serological response to EDSV is observed at least until 74 weeks post vaccination.

In study 2, two groups of 30 16-week old SPF hens were included: one group was vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccine and the other was not vaccinated. At the age of 53 weeks, hens were divided into 3 pens per group. Just before challenge, at 60 weeks of age, blood samples were collected. All hens were challenged with the EDSV M13 strain. Egg production and quality was monitored from 21 until 64 weeks of age. In the control group, egg production fell consistently and significantly following challenge. On average, egg production in the vaccinated group was 45% higher compared to the control group and this difference was statistically significant. After challenge, the fraction of abnormal eggs in the control group was 6.8 times as high as in the vaccinated group and this difference was statistically significant. The study supports a duration of immunity of 44 weeks (60 weeks of age) for protection against egg drop due to EDSV.

Study 3 was designed identically to study 2 described above, but for the timing of the challenge at 98 weeks of age. Vaccinated animals had an average of 6.8 log₂ EDSV HI titre before challenge. After challenge, the egg production of the vaccinated group was not negatively affected. For the non-vaccinated treatment group, egg production went down following challenge and recovered towards the end of the observation period. On average, post-challenge egg production in the vaccinated group was 54% higher compared to the non-vaccinated control group and this difference was statistically significant. The percentage of abnormal eggs increased both in the vaccinated group and in the non-vaccinated group; no significant differences were observed between groups. The study supports a duration of immunity of 82 weeks post vaccination for protection against egg drop due to EDSV. It is noted that protection was not complete, since an increase in abnormal eggs was seen in the vaccinated group after challenge. This is however considered compatible with the claimed reduction in egg drop and eggshell defects.

In conclusion, the claimed DOI of 80 weeks post vaccination for EDSV is supported by the results of challenge at 82 weeks post vaccination and by serology up to 74 weeks post vaccination.

Maternally derived antibodies (MDA)

No studies were performed. This is accepted since at the age of vaccination MDAs are no longer relevant.

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.'

Clinical trials

Four clinical trials were performed in the Netherlands. In these experiments, the safety and efficacy of Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS was evaluated under clinical conditions. The

general set-up of the studies is described in the dossier. In these four studies blood samples were collected and serological data were generated in 4 separate studies. In order to substantiate efficacy claims, 5 challenge experiments were performed in the laboratory with animals vaccinated in the field. The set-up of these studies and the results are discussed below for each virus.

AMPV

In study 1 serology was performed on samples taken during the first field study (refer to section 3). Commercial layers in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Blood samples were collected from at least 20 birds per flock at 12, 16, 18 and 22 weeks of age and then every 10 weeks until the end of the production period (approximately 86 weeks of age). Approximately 100 hens from the test flock were kept until 102 weeks of age and additional bleeds were taken from 20 birds at 92 and 102 weeks of age. Antibodies were detected against TRT (turkey rhinotracheitis). The test is considered valid since at 12 weeks of age (time of vaccination) all birds were seronegative for AMPV. The antibody profiles were similar for control and test groups.

In study 2 serology was performed on samples taken during the second field study (refer to section 3). Commercial layers in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Blood samples were collected from 20 birds per flock at 12, 16, 18 and 22 weeks of age and then every 10 weeks until 92 weeks and at 100 weeks of age. Antibodies were detected against TRT. The test is considered valid since at 12 weeks of age (time of vaccination) all birds were seronegative for AMPV. It can be concluded that in the test flock antibodies were detected up to the end of the study whereas the control flock remained seronegative.

In study 3 serology was performed on samples taken during the third field study (refer to section 3). Breeders in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

At 14, 19, 21, 25, 35, 45, 56, and 60 weeks of age blood samples were taken from 20 randomly selected hens in each group. Before the study birds went to slaughter in week 60, approximately 100 birds from each flock were transferred to a research centre and were kept until they were approximately 84 weeks of age. Blood sampling from 20 selected tagged hens per flock was carried out at approximately 5-week intervals. TRT antibodies were detected. Test and control birds had been both primed with Nobilis Rhino CV at 5 weeks of age. This did not result in significant serological responses. After booster with either of the inactivated combination vaccines, responses to AMPV were similar in both groups and detectable up to 84 weeks of age. The data are however indicative of a field challenge between weeks 25 and 35 (and possibly between weeks 56 and 62). There were, however, no clinical signs of AMPV recorded nor was the performance of the birds affected in this study which is indicative of vaccine protection against AMPV. Little can be concluded on the OOI or DOI based on these data.

In study 4 serology was performed on samples taken during field study 4 (refer to section 3). Breeders in the two groups were vaccinated with various vaccines as per the farm vaccination scheme.

Test and control birds were both primed with Nobilis Rhino CV at 5 weeks of age. This did not result in significant serological responses. After booster with either of the inactivated combination vaccines, responses to AMPV were similar in both groups and detectable up to 55 weeks of age. The data are however indicative of a field challenge between weeks 35 and 55. Little can be concluded on the OOI or DOI.

Study 5 was performed using layers from the second field study, 30 from each group. At 94 weeks of age (82 weeks post vaccination) birds were challenged with AMPV and monitored for clinical signs. Average log₂ anti-AMPV titres before and after challenge were 3.49 and 3.88 in the test group and 3.0 and 3.32 in the control group. Following challenge, egg production was stable at >80%, with no obvious differences between the test vaccinated and control groups. Further, no clinical signs of AMPV infection were observed and no virus was detected at any time point from any of the tracheal swabs from either experimental group. The study was considered invalid.

In conclusion, serology indicates a similar antibody response is achieved after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing a TRT component when applied in commercial vaccination schemes in layers or breeders.

IBV

The set-up of studies 1-4 is described above for AMPV. IBV M41 and IBV 4/91 titres were also determined in these studies. Antibody profiles for test and control layer flocks were similar for both IBV antigens.

In conclusion, the antibody responses to IBV M41 and IBV 4/91 antigens were very similar after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing an IBV component when applied in commercial vaccination schemes in layers or breeders. It is noted that birds of test and control flocks were primed with various combinations of live IBV vaccines, in accordance with the proposed use of Nobilis Multiriva RT+IBm+ND+EDS as a booster vaccine.

NDV

The set-up of studies 1-4 is described above for AMPV. NDV la Sota and Ulster HI titres were also determined in these studies. Test and control birds were vaccinated with Innovax-ND-IBD and Nobilis ND C2 prior to the test vaccine or control vaccine. Antibody profiles for test and control layer flocks were similar for both NDV antigens in all studies.

In study 5, two groups of 15 test or control vaccinated layers from field study 1 and 15 non-vaccinated SPF birds were included. Challenge was performed with NDV Herts 33/56 at 30 weeks of age. All SPF birds were affected with NDV and euthanised within 4 days. None of the vaccinated birds showed any symptoms of NDV infection. Vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccine within the commercial vaccination scheme used, including prior vaccination with Innovax ND IBD and Nobilis ND C2, provided full protection against NDV challenge at 18 weeks post vaccination.

Study 6 was performed using fifteen 65-week-old commercial broiler breeders taken from field study 4. The hens had been vaccinated with Nobilis ND C2 at 2 weeks of age, Nobilis ND Clone 30 at 8 weeks of age and Nobilis Multiriva RT+IBm+ND+EDS+Gm+REOm at 15 weeks of age. An additional group of 15 100-week-old SPF birds was used as unvaccinated controls. Challenge was performed at 65 weeks of age with NDV Herts 33/56, and birds were monitored for clinical signs for 21 days thereafter. All SPF birds were affected by NDV and euthanised within 4 days. None of the vaccinated birds showed any NDV-related symptoms during the observation period. Vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccine within the commercial vaccination scheme used, including prior vaccination with Nobilis ND C2 and Nobilis ND Clone 30, provided full protection in breeders against NDV challenge at 50 weeks post vaccination.

Study 7 was set up as follows: fifteen 76-week-old commercial layers were taken from field study 2. The hens had been vaccinated with Innovax-ND-IBD at one day of age, Avinew NEO at 3 weeks of

age, Nobilis ND Clone 30 at 7 weeks of age and Nobilis Multiriva RT+IBm+ND+EDS+Gm+REOm at 12 weeks of age. An additional group of fifteen 60-week-old SPF birds was used as unvaccinated controls. Challenge was performed at 76 weeks of age with NDV Herts 33/56, and birds were monitored for clinical signs for 21 days thereafter. Twelve out of thirteen control birds were affected by the challenge and euthanised within 4 days (92%). One bird in this group was alive and healthy at day 3 post challenge and had to be euthanised on welfare ground and was scored as 'protected'. In the vaccinated group, one bird showed ND-related signs on day 13 post challenge and was euthanised, resulting in 93% protection. Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS vaccine applied within the commercial vaccination scheme used, including prior vaccination with live NDV vaccines, provided full protection in layers against NDV challenge at 64 weeks post vaccination.

In conclusion, the onset, duration and magnitude of the anti-NDV antibody response cannot be attributed to vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS alone. A booster-effect was observed in the antibody titres from 4 weeks post vaccination with the test vaccine. Titres achieved were relatively stable up to 102 weeks of age and similar in flocks vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS or existing inactivated viral vaccines from the Nobilis range. Challenge studies show that birds vaccinated according to a commercial vaccination schedule, including various priming vaccinations for NDV and booster with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS, were significantly protected from velogenic NDV challenge until 76 weeks of age (64 weeks post vaccination).

EDSV

The set-up of study 1 including the vaccination schedule for field study 1 is described above for AMPV. Evaluation of EDSV titres was performed and antibody titres for test and control flocks were similar. An average titre of 6.7 log₂ at 4 w.p.v. and 3.6 log₂ at 90 w.p.v. was detected in the test flock.

The set-up of study 2 including the vaccination schedule for field study 2 is described above for AMPV. Evaluation of EDSV titres was performed. The non-vaccinated control flock remained seronegative. An average titre of 7.0 log₂ at 4 w.p.v. and 5.4 log₂ at 88 w.p.v. was detected in the test flock.

The set-up of study 3 including the vaccination schedule for field study 3 is described above for AMPV. Evaluation of EDSV titres was performed. The non-vaccinated control flock remained seronegative. An average titre of 3.9 log₂ at 5 w.p.v. and 3.4 log₂ at 70 w.p.v. was detected in the test flock.

The set-up of study 4 including the vaccination schedule for field study 4 is described above for AMPV. Evaluation of EDSV titres was performed. Antibody titres in the control group remained close to the detection limit throughout the study. In the test group a response to vaccination is observed, albeit low. Antibodies remained detectable until 40 weeks post vaccination.

In study 5 commercial layer hens from field trial 1, vaccinated with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS at the age of 12 weeks were included when they were 69 weeks of age (n=30). Unvaccinated commercial layer hens were also obtained from the field (16 week of age) as non-vaccinated challenge controls (n=30). Birds were housed in 3 pens of 10 animals per group. Egg production and egg quality was monitored. All birds were challenged with the EDS M13 strain; the vaccinated group was 74 weeks of age and the control group 21 weeks of age. The study is considered valid since a clear effect on egg production and quality was observed in non-vaccinated birds after challenge. The use of younger birds as control group is considered justified; this can be viewed as a worst-case scenario since these birds have a higher laying percentage compared to birds at 74 weeks of age. The laying percentage after challenge was significantly higher in the

vaccinated birds. The results support efficacy of the vaccine in commercial layer birds, with a duration of immunity of 62 weeks after vaccination.

Overall conclusion on efficacy

AMPV

The proposed indication for AMPV is reduction of egg drop caused by avian metapneumovirus. The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 80 weeks post vaccination. In total, five studies were performed to determine onset and duration of immunity against AMPV. After vaccination, antibodies to AMPV were detected from 5 weeks after vaccination (first sample) and persisted at consistent level for up to 84 weeks after vaccination. The AMPV titres after vaccination with Nobilis Multiriva were notably higher in birds primed with Nobilis Rhino CV, compared to titres in non-primed birds. The conclusion for the first two experiments in which birds were challenged at 26 or 60 weeks of age was that the challenge was too weak, and the studies were invalid. The applicant's reasoning not to repeat the challenge studies for the 26 and 60 weeks timepoints is accepted. The vaccine was shown to provide protection at 80 weeks post vaccination. Average antibody titres $\geq 3.6 \log_2$ can be considered related to protection and serology can be used to support onset and duration of immunity. The totality of data is considered to support the claim for reduction of egg drop caused by avian metapneumovirus, with an onset of immunity of 5 weeks post vaccination and a duration of immunity of 80 weeks post vaccination.

In the four clinical trials, layer pullets and broiler breeders were vaccinated under field conditions (receiving the standard vaccination program, with or without the test vaccine). AMPV serology indicates a similar antibody response is achieved after vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS compared to licensed inactivated Nobilis vaccines containing a TRT component. A challenge study with AMPV was performed on birds derived from one of the clinical studies but the study was invalid, and no conclusions could be drawn.

IBV

The proposed indication for IBV is reduction of respiratory signs and egg drop caused by infectious bronchitis virus, strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), var2 (GI-23 genotype) and Q1 (GI-16 genotype). The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 100 weeks of age. A serological response was observed from 4 weeks post vaccination and can be reliably concluded to last for 75 weeks post vaccination.

For the use of Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS as a booster, after priming with live IBV M41 and IBV 4/91 vaccines (at day of age), the efficacy against IBV M41 and 4/91 challenge is supported by data at 45 and 81 weeks post vaccination. In addition, efficacy of the prime-boost regimen against QX and Var2 challenge at 25 weeks post vaccination was shown. Efficacy against IBV Q1 was shown at 11 weeks post vaccination. The serological and challenge data together support the claimed OOI of 4 weeks and DOI of 80 weeks for IBV (M41 and 4/91), with cross-protection against QX, Q1 and Var2 strains.

The applicant has provided an overview of all the clinical data recorded in the IB vaccination-challenge studies. From this data it can be concluded that vaccination with a prime-boost scheme resulted in a reduction of coughing and respiratory clinical signs. Thus, protection against respiratory signs caused by IB M41, IB 4-91, IB QX and IB Var2 is considered adequately supported by data.

Serological analysis of the clinical trials shows that the antibody responses to both IBV M41 and 4/91

were very similar in vaccinated groups compared to control vaccinated groups. It is noted that in all four clinical studies, birds of both test and control flocks were primed with various combinations of live IB vaccines at more than one timepoint prior to vaccination with the inactivated vaccine, as per the proposed use.

NDV

The proposed indication for NDV is reduction of mortality and clinical signs caused by NDV. The claimed onset of immunity is 4 weeks post vaccination and the duration of immunity 80 weeks post vaccination. One serological study and four vaccination-challenge studies were performed in order to support OOI and DOI against NDV. Serology showed a response to vaccination from 4 weeks with measurable titres lasting at least until 88 weeks post vaccination. Priming with live ND vaccines resulted in consistently higher antibody titres. A challenge study performed in accordance with Ph. Eur. 0870 requirements showed that the vaccine blended at 100%, 75% or 50% complies with the test. Further challenge studies support the claimed OOI of 4 weeks and the DOI of 80 weeks post vaccination. This protection was achieved both with and without priming of birds with live ND vaccines.

In the four clinical trials birds were primed with various combinations of ND vaccines at more than one timepoint prior to vaccination with the test or control vaccine. Therefore, the onset, duration and magnitude of the anti-NDV antibody response cannot be attributed to vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS alone. A booster-effect was observed in the antibody titres from 4 weeks post vaccination with test or control vaccines. Titres achieved were relatively stable up to 102 weeks of age and similar in test and control groups. Challenge studies in birds derived from the clinical trials showed that birds vaccinated according to a commercial schedule were significantly protected from velogenic NDV challenge at 30, 65 and 76 weeks of age (i.e. up to 64 weeks post booster vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS).

EDSV

The proposed indication for EDSV is reduction of egg drop and eggshell defects caused by egg drop syndrome '76 virus, with an onset of immunity of 4 weeks post vaccination and a duration of immunity of 80 weeks post vaccination. In total 5 studies were performed, one serological study and 4 challenge studies.

While there is no direct evidence for the claimed onset of immunity of 4 weeks post vaccination for EDSV, based on the serological response observed it can be accepted that a response to vaccination has developed by 4 weeks post vaccination that is expected to confer protection. Duration of immunity is supported by the results of challenge at 82 weeks post vaccination and by serology up to 74 weeks post vaccination. The claimed duration of immunity to EDSV of 80 weeks post vaccination is supported by data.

In the clinical trials EDSV antibody titres were induced by vaccination with Nobilis Multiriva RT+IBm+ND+Gm+REOm+EDS and these remained detectable for up to 87 weeks post vaccination in layer type birds and up to 73 weeks post vaccination in broiler breeders. Laboratory challenge of commercial layer birds at 62 weeks post vaccination confirms protection as observed in pre-clinical studies.

No studies were performed to investigate interference by maternally derived antibodies. This is considered justified since at the age of vaccination MDAs are no longer relevant.

Part 5 – Benefit-risk assessment

Nobilis Multiriva RT+IBm+ND+EDS is an inactivated vaccine for chickens containing avian metapneumovirus strain BUT1 #8544, avian infectious bronchitis virus strain M41, avian infectious bronchitis virus strain 4/91, Newcastle disease virus strain Ulster, and egg drop syndrome 1976 virus strain BC14, and light liquid paraffin as adjuvant. The active substances are known substances.

The vaccine is presented as an emulsion for injection in packs containing 1 bottle of 300 ml (1000 doses) or 600 ml (2000 doses) and is to be administered intramuscularly as a single dose of 0.3 ml in the breast or thigh region from 8 weeks of age onwards, but no later than 3 weeks before the onset of lay. The proposed withdrawal period is zero days.

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

For the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus,
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus strains Massachusetts (GI-1 genotype), 4/91-793B (GI-13 genotype), QX – D388 (GI-19 genotype), Var2 (GI-23 genotype) and Q1 (GI-16 genotype),
- reduction of mortality and clinical signs caused by Newcastle disease virus,
- reduction of egg drop and eggshell defects caused by egg drop syndrome 1976 virus

The application has been submitted through the centralised procedure under Article 42(4) of Regulation (EU) 2019/6 (**optional scope**) and in line with the requirements for submissions under Article 8 of Regulation (EU) 2019/6 – full application.

Benefit assessment

Direct benefit

The proposed benefit of Nobilis Multiriva RT+IBm+ND+EDS is its efficacy against AMPV, IBV, NDV and EDSV, which was investigated in a large number of well-designed pre-clinical and clinical studies conducted to an acceptable standard. The results generally support the claimed efficacy with an onset of immunity of 4 weeks post vaccination (5 weeks for AMPV) and a duration of immunity of 80 weeks post vaccination when the vaccine is used as a booster after priming with live or inactivated vaccines against IBV.

Additional benefits

Nobilis Multiriva RT+IBm+ND+EDS is a comparatively large combination of inactivated viral components, reducing the need for the application (injection) of different vaccines within a short timeframe. Compared to existing inactivated viral vaccine combinations, the dose volume is smaller which is an advantage with respect to injection-site safety and animal welfare.

Risk assessment

Quality

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. Quality data for each of the antigens are included in the respective vaccine

antigen master files. 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. The whole production process was evaluated at production scale and shown to be consistent. The data provided support the proposed 24-month shelf life.

Safety

Measures to manage the risks identified below are included in the risk management section.

Risks for the target animal

Administration of Nobilis Multiriva RT+IBm+ND+EDS in accordance with SPC recommendations is generally well tolerated.

The safety of the vaccine in chickens at 7 weeks of age was confirmed in a GLP safety study and four clinical trials. The main reported adverse reaction is injection site swelling that was observed in some animals after being administered the standard dose. However, the effects were mild and transient.

Risk for the user

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice for veterinary medicinal products containing mineral oil is included in the SPC.

Risk for the environment

Nobilis Multiriva RT+IBm+ND+EDS is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk for the consumer

The product is not considered to pose a risk to consumer safety. Based on the components, residue studies are not required. The withdrawal period is set at zero days.

Special risks

None identified.

Risk management or mitigation measures

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

User safety

User safety risks have been identified. These risks have been addressed by the safety warnings included in the SPC.

Environmental safety

No specific environmental safety risks have been identified. Standard advice on waste disposal is included in the SPC.

Conditions or restrictions as regards the supply or safe and effective use of the VMP concerned, including the classification (prescription status)

The veterinary medicinal product is subject to a veterinary prescription.

Official control authority batch release may be required for this product according to national requirements.

Evaluation of the benefit-risk balance

Following evaluation of the data, the CVMP agreed that the indication should be:

“For the active immunisation of chickens for:

- reduction of egg drop caused by avian metapneumovirus (AMPV)
- reduction of respiratory signs and egg drop caused by infectious bronchitis virus (IBV) strains Massachusetts (GI-1 genotype) and 4/91-793B (GI-13 genotype)
- reduction of mortality and clinical signs caused by Newcastle disease virus (NDV)
- reduction of egg drop and eggshell defects caused by eggdrop syndrome-1976 virus (EDSV).

Onset of immunity:

- IBV, NDV and EDSV: 4 weeks post-vaccination
- AMPV: 5 weeks post-vaccination

Duration of immunity:

- AMPV, IBV, NDV and EDSV: 80 weeks post-vaccination

Cross-protection has been established for IBV strains QX-D388 (GI-19 genotype), Var2 (GI-23 genotype) and Q1 (GI-16 genotype).”

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 balance is considered positive.

Conclusion

Based on the original and supplementary data presented on quality, safety and efficacy, the Committee for Veterinary Medicinal Products (CVMP) considers that the application for Nobilis Multiriva RT+IBm+ND+EDS 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.