FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS
14 rue Claude Bourgelat
Parc d'activités de la Grande Marche - Javené
BP 90203
35302 Fougères Cedex
France

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR AN IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

DINDORAL

MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0485/001/MR
Name and pharmaceutical form	Dindoral Lyophilisate for oral suspension
Applicant	Boehringer Ingelheim Animal Health France
Active substance(s)	Attenuated avian Adenovirus group II, Domermuth strain
ATC Vetcode	QI01CD
Target species	Turkeys and pheasants
Indication for use	In turkeys from the age of 4 weeks: active: immunisation against the haemorrhagic enteritis. In pheasant from the age of 4 weeks: active immunisation against the marble spleen disease.

MODULE 2

The Summary of Product Characteristics (SPC), the labelling and package leaflet for this immunological veterinary medicinal product (IVMP) are available in the Union Product Database (UPD).

The Summary of Product Characteristics (SPC) for this product is available on the website http://www.anmv.anses.fr/

MODULE 3

SUMMARY OF ASSESSMENT

Legal basis of original application	Full application in accordance with Article 8 of Regulation (EC) 2019/6 as amended.
Date of completion of the original mutual recognition procedure	11/12/2023
Date immunological veterinary medicinal product first authorised in the Reference Member State (MRP only)	28/11/1986
Concerned Member States (CMS) for original procedure	IT, ES
CMS for subsequent use procedure	NA
Withdrawn CMS during original mutual recognition	ES The company decided to withdraw the application. At the time of withdrawal, the MS (ES) considered that the data provided did not allow concluding on a positive benefit-risk balance.

1. SCIENTIFIC OVERVIEW

The IVMP is manufactured and controlled using validated methods and tests that ensure the consistency of the IVMP released on the market.

The IVMP can be safely used in the target species.

The IVMP is also safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC.

The efficacy of the IVMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation for this IVMP.

2. QUALITY DOCUMENTATION (physicochemical, biological or microbiological information)

2.A. Product description

The IVMP contains attenuated avian adenovirus group II (Domermuth strain) (QS : 9/10 seroconversion*), skimmed milk, sodium glutamate and water for injection.

The IVMP is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The container/closure system is made of type I glass bottle closed with butyl elastomer stopper and aluminium cap.

The choice of the vaccine strain and formulation as well absence of preservative is justified.

The selection of the manufacturing process of the active substance and the finished product is explained.

* One seroconversion must be obtained on at least 9 SPF chickens aged 2-3 weeks out of 10 vaccinated (ELISA test).

2.B. Description of the manufacturing method

The IVMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Manufacturing process is described, the active ingredient being a suspension of live virus multiplied in turkey-poults.

Process validation data on the IVMP are provided in accordance with the relevant European guidelines.

2.C. Production and control of starting materials

The active substance is the Domermuth strain of the live attenuated Adenovirus group II, an established active substance which is naturally avirulent.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification are provided.

Scientific data are provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products was satisfactorily demonstrated.

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs or in-house specifications.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately screened for the absence of extraneous agents according to the Ph. Eur. and European guidelines; any deviation is adequately justified.

The master and working seeds were produced according to the seed lot system as described in the relevant guideline(s).

2.D. Control tests during the manufacturing process

The tests performed during production are described and the results of three consecutive runs, conforming to the specifications, are provided.

In-process control tests are carried out on intermediate stages of manufacture in order to verify the consistency of the manufacturing process and the final IVMP.

A specification was set for each intermediate and the analytical methods are described and validated, if applicable.

2.E. Control tests on the finished product

For all tests, a short description of the techniques for analysing the finished product is provided. The tests and their specifications and limits are justified and are considered appropriate to adequately control the quality of the IVMP.

Satisfactory validation data for each analytical methods are provided, if appropriate.

The tests performed on the final product conform to the relevant requirements and monographs, if applicable; any deviation from these requirements is justified.

The potency test is based on serological method and ELISA.

Batch analytical data from the proposed production site(s) are provided demonstrating compliance with the determined specification.

2.F. Batch-to-batch consistency

Full protocols of four consecutive batches of the product, representative of the routine production and giving the results for all tests performed during production and on the finished product, are provided in order to ensure that quality is consistent from batch to batch and to demonstrate conformity with the predefined specifications.

2.G. Stability tests

Stability data on the active substance(s) are provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product are provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

The in-use shelf life of 3 hours of the reconstituted vaccine is supported by the data provided. The recommendations in the product leaflet should be followed.>

3. SAFETY DOCUMENTATION (safety and residues tests)

3.A. General requirements

The safety of the IVMP when administered to the target species, the potential harmful effects (residues in IVMP, substance in foodstuff), the potential serious risk for human beings during product administration and to the environment are adequately described.

Studies were performed using either the Domermuth strain or batches (commercial or experimental).

3.B. Pre-clinical studies

The safety of the administration of one dose, an overdose (only for live IVMP) and the repeated administration of one dose to the target animal was demonstrated in SPF and commercial turkey, aged of 4 weeks or older and vaccinated by oral route. They were observed for a minimum of 19 days. Haemorrahagic enteritis lesions, spleen weight and spleen viral presence were followed. Also a study in pheasant, 8 weeks old, was performed. No adverse event was recorded.

No investigation of effects on the reproductive performance was conducted because the vaccine is not intended for this category of animals.

Effect of the vaccine on the immune response of the vaccinated animals was investigated in one study, in 5 weeks old SPF turkeys, with a follow-up based on the antibodies response to another vaccination and on the histological modifications of the lymphoid organs. The vaccine strain has an effect on the immunological functions as indicated in the section 3.6 of SPC, which is not higher than the wild strain.

A study was performed in 2 weeks old seronegative commercial turkey to investigate the spread and the dissemination of the vaccine strain. The results showed that the vaccine strain spread to in-contact birds and disseminate to spleen of vaccinated birds.

An another study performed in 2 weeks old aimed to investigate the spread, the dissemination and also the increase of virulence of the vaccine strain. The study showed that the vaccine strain remains non virulent over 7 passages in naïve and of minimum age turkeys which supports the absence of reversion to virulence of the vaccine strain.

The SPC contains the relevant information with respect to the spread and dissemination capacities of the vaccine strain and the effect on the immune response. Since the vaccine is shed by the vaccinated animals, also warnings with respect to the administration of the vaccine are also inserted into the SPC for the person who administers the vaccine.

The excipients used does not require any withdrawal period is necessary.

No specific assessment of the interaction of this product with other medicinal product was made. Therefore, an appropriate warning in the SPC is included.

3.C. Clinical trials

A field trial in two commercial farms in Italy was performed, in which 7000 female one day old turkeys and 4000 male one day old turkey were vaccinated. General health, mortality and growth of the birds were followed. The safety of the vaccine was supported.

3.D. Environmental Risk Assessment

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline, which showed that no further assessment is required. The assessment concluded that no warnings are therefore required.

4. EFFICACY DOCUMENTATION

4.A. General requirements

All pre-clinical and clinical studies performed to support the efficacy profile of the vaccine were carried out in seronegative turkeys aged between 2 and 6 weeks.

The batches used were manufactured according to the analytical dossier.

The evidence justifying the use of Dindoral in pheasant is coming from the published literature.

4.B. Pre-Clinical Studies

The efficacy of the product was demonstrated in laboratory studies under well-controlled conditions in accordance with the relevant requirements, which show that the indications and vaccine scheme included in the SPC are supported.

Production of post-vaccinal antibodies was shown in a preliminary study involving 6 weeks old turkey poults.

Two studies were carried out to support the onset and the duration of immunity.

The “onset of immunity” study was performed in six weeks old turkeys (groups of fourteen birds) either unvaccinated and challenged with a THEV virulent strain, or vaccinated and challenged. After the challenge, the birds were followed for clinical signs and mortalities and at the end of the study the animals were sacrificed for spleen weighting, antigen testing and observation of splenic and intestinal lesions. Results showed that two weeks post vaccination, none of the vaccinated birds were dead and had splenic or intestinal lesions. There were all negative for THEV antigen and there was a statistically significant difference in the mean spleen weight between the vaccinated and the unvaccinated birds. The study thus supports an onset of immunity of 2 weeks.

The “duration of immunity” study was performed in 30 days old turkey poults (groups of 10 birds). The birds were either vaccinated or unvaccinated and

challenged at either 21 days post vaccination or 56 days post vaccination. They were followed daily for clinical signs and four days after challenge they were sacrificed for spleen weighting and detection of THEV antigens. No clinical signs were observed post-challenge in the vaccinated animals and none of them presented specific THEV lesions in spleen nor THEV antigen. The spleen of the unvaccinated birds were statistically heavier than those of the vaccinated animals. The study thus supports a duration of immunity of 8 weeks and the minimal age for vaccination.

No study of the influence of the maternal antibodies was performed since the vaccination is recommended from 4 weeks of age when the maternal antibodies have not interference.

No study on interactions was performed so the SPC contains a specific warning.

4.C. Clinical trials

Efficacy of vaccination was also demonstrated under field conditions in a controlled field trial including 7000 female and 4000 male vaccinated animals and 7000 female and 4000 male controls on two farms. Clinical signs of the disease, presence or absence of the THEV in birds and clinical and macroscopical lesions of spleen and duodenum, histological lesions of the spleen were followed. During the study none of the birds had any signs of the disease. The mean total clinical and macroscopic lesions scores of the vaccinated birds were first higher than those of the control group during the first week and became lower one week after the vaccination. The vaccine strain was found in the spleen and the cloacal swabs of the vaccinated animals from 7 days post vaccination until the end of the study. A field strain passage was observed on both farms :

- control animals : spleen and swabs samples positive from 35 days and 42 days on farm 1 and 2 respectively

- vaccinated animals : spleen and swabs samples positive from 35 days and 42 days on farm 1 and 2 respectively with a lower number of positive samples in those groups

The study supported the efficacy of the vaccine.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment are acceptable.