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PUBLICLY AVAILABLE ASSESSMENT REPORT

FOR THE IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

AviPro AE
suspension for use in drinking water for chickens

PRODUCT SUMMARY

EU procedure number	DE/V/0292/001/MR
Name and pharmaceutical form	AviPro AE Suspension for use in drinking water for chickens
Applicant	Lohmann Animal Health GmbH Heinz-Lohmann-Straße 4 27472 Cuxhaven Germany
Active substance(s)	Live avian encephalomyelitis virus, strain 1143 Calnek
ATC vetcode	QI01AD02
Target species	Chickens
Indication for use	For active immunisation of future layers and breeding chickens from 10 weeks of age against avian encephalomyelitis virus, to prevent vertical transmission of avian encephalomyelitis virus and to induce passive immunity in embryos and young chickens against infection with avian encephalomyelitis.

PRODUCT INFORMATION

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).

SUMMARY OF ASSESSMENT

Legal basis of original application	National marketing authorisation in Germany in accordance with Directive 81/851/EEC (authorisation date 20/07/1999)
Date of completion of the original mutual recognition procedure	14/12/2021
Date immunological veterinary medicinal product first authorised in the Reference Member State (MRP only)	14/12/2021
Concerned Member States (CMS) for original procedure	AT, ES, FR
CMS for subsequent use procedure	--
Withdrawn CMS during original mutual recognition procedure	--

1. SCIENTIFIC OVERVIEW

Avian encephalomyelitis (AE), caused by avian encephalomyelitis virus (AEV), is considered as an important and widespread neurotropic disease in poultry. AEV can be transmitted vertically or horizontally, and causes clinical signs including paralysis, ataxia and paresis, muscular dystrophy, and subsequently blindness in young chicks. Infection of susceptible laying hens is mainly subclinical and can result in a reduction in egg production and hatchability. After recovery from infection, the birds are protected and maternally derived antibodies (MDAs) can provide protection against AEV in offspring. Consequently, in regions where AE is prevalent it is recommended to vaccinate pullets shortly before the onset of the laying period.

AviPro AE is intended for active immunisation of future layers and breeding chickens from 10 weeks of age against AEV, and to prevent vertical transmission of AEV and to induce passive immunity in embryos and young chickens against infection with AEV.

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

The IVMP can be safely used in the target species.

The IVMP is also safe for the user, 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 micro-biological information)

2.A. Product description

AviPro AE is a liquid live vaccine for the active immunisation of chickens against avian encephalomyelitis by drinking water and contains the virus strain 1143 Calnek ($10^{3.0}$-$10^{4.5}$ EID_{50}/dose). The antigen is stabilized by addition of lactose phosphate buffer (disodium phosphate dehydrate, lactose monohydrate, and potassium dihydrogen phosphate) and skimmed milk solution (skimmed milk powder and water for injections). No adjuvant or preservatives are included. For administration of the vaccine, the vaccine suspension is dissolved in water.

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

The vaccine is filled in glass bottles (Ph. Eur. Type I) with a beaded rim and closed with a chlorobutyl elastomer closure. The bottles are sealed with aluminium tear-off caps.

The choice of the vaccine strain and the formulation of the vaccine is justified. The selection of the manufacturing process of the active substance and the finished product is explained.

Characterisation of the active substance including the determination of biological properties, biological activity, immunochemical properties, purity and impurities of the active substance is provided in order to allow suitable specifications to be established.

2.B. Description of the manufacturing method

The virus strain is grown in SPF chicken eggs. The IVMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the IVMP are provided in accordance with the relevant European guidelines. The product is manufactured in accordance with the European Pharmacopoeia (Ph. Eur.) and relevant European guidelines.

2.C. Production and control of starting materials

The active substance is AEV strain 1143 Calnek, an established active substance described in the Ph. Eur. Monograph 0588.

The starting materials used for this vaccine are adequately controlled and comply to Ph. Eur. or in-house-specifications.

Scientific data and/or certificates of suitability issued by the EDQM 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.

Biological starting materials used are in compliance with the relevant Ph. Eur. monographs and guidelines and are appropriately assessed for the absence of extraneous agents according to Ph. Eur. Monograph 5.2.5. The master and working seeds were produced according to the seed lot system as described in Ph. Eur. Monograph 0062.

Starting materials of non-biological origin used in production comply with corresponding Ph. Eur. monographs or in-house specifications.

Batch analytical data demonstrating compliance with the determined specifications are provided.

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.

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

A shelf life and storage conditions for the intermediate IVMP are defined based on data resulting from stability studies.

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 method 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.

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

2.F. Batch-to-batch consistency

The demonstration of the batch-to-batch consistency is based on the results of three final product batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

Full protocols of the three consecutive batches of the final product are provided.

2.G. Stability tests

Stability data on the finished product are provided in accordance with applicable European guidelines, demonstrating the stability of AviPro AE throughout its shelf life of 1 year when stored under the approved conditions.

The in-use shelf life of 2 hours of the diluted vaccine is supported by the data provided. The recommendations in the product leaflet should be followed by the user.

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.

The safety of AviPro AE was investigated for initial product registration in the 1980s and 1990s according to the relevant regulatory guidelines of this time, namely Commission Directive 92/18/EEC, Ph. Eur. 0588 (2nd edition of 1988 and 3rd edition of 1997) and GLP. Additional laboratory safety studies were performed in 2012 according to Directive 2001/82/EC as amended by Directive 2004/28/EC and updated Annex I to the Directive (2009/9/EC), Ph. Eur. 0062, Ph. Eur. 5.2.6, Ph. Eur. 0588 and CVMP/VICH/595/98 VICH Topic GL Step 7 – Guidelines on Good Clinical Practice (GCP).

For most batches produced in the 1990s no documentation is available anymore at the applicant's archive, but the applicant confirms that the batches used for the safety studies were manufactured according to the description of the manufacture provided in Part 2 of this dossier. Documentation on the master seed virus (MSV) is included in Part 2 of the dossier.

3.B. Pre-clinical studies

The safety of the administration of one dose and an overdose to the target animal was demonstrated in several laboratory studies:

Three single-dose-studies were performed in 21 to 28-day-old as well as in 11-weeks old SPF-chickens by the recommended oral route, using the MSV resp. one batch of AviPro AE at minimum effective dose up to one maximum dose. None of the chickens showed any clinical signs or died following vaccination during the observation period as per the requirements of the Ph. Eur. 0588 valid at the time when the respective studies were performed.

Thus, the oral application of up to one maximum dose of AviPro AE to SPF chickens of recommended age is considered safe.

A test on limited pathogenicity was performed in 1-day-old SPF-chickens by the intracerebral route, using the MSV in different dilutions. The vaccine did not cause any clinical signs or death during the 9 days after infection as per the requirements of the Ph. Eur. 0588 valid at the time when the respective study was performed.

Thus, the MSV can be considered of limited pathogenicity for 1-day-old SPF chickens.

Four overdose-studies were performed in 3-weeks-old SPF-chickens by the recommended oral route, using batches of AviPro AE at one maximum dose up to a 10-fold maximum dose. Additionally, four studies regarding extraneous agents using chicks were performed in 2-weeks-old SPF-chickens by combined intramuscular/eye drop application using batches of AviPro AE resp. the MSV at up to 100-fold maximum dose twice, leaving an interval of two weeks between. None of the chickens showed any clinical signs or died following vaccination during the observation period.

Thus, the oral application of up to one 10-fold maximum dose as well as the combined intramuscular/eye-drop application of up to a 100-fold maximum dose twice of AviPro AE to SPF chickens of recommended age is considered safe.

The repeated administration of AviPro AE is not part of the recommended vaccination scheme; therefore, no study is required.

Effects on the reproductive performance were examined by Calnek et al, 1961 in 11-month-old breeder chickens and their progeny. Vaccinated hens could transmit the virus to their

progeny resulting in AE specific clinical signs. The percent of chicks developing clinical signs depends on the time of hatch post vaccination.

Thus, the eggs up to 4 weeks post vaccination should not be used for hatching and the recommended time of vaccination up to 4 weeks prior beginning of laying period is well defined.

One specific study was provided for the examination of immunological functions. The study was performed in 20-weeks old SPF-chickens by the recommended oral route, using one batch of AviPro AE at minimum effective dose and one dose of one batch of TAD Thymo vac. Chicken anaemia virus (CAV) specific neutralizing antibodies were induced in both groups of chickens, vaccinated or not in addition with AviPro AE.

Thus, the vaccine is not immunosuppressive, as it does not affect the immune response when administered together with a vaccine against chicken anaemia. Moreover, based on literature, the AE virus does not affect lymphoid organs and tissues and therefore it is to expect that AviPro AE has no effect on the immunological functions.

For the live virus strain included in the vaccine, specific studies were carried out or scientific publications were presented to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain:

Spread was examined in one contact-study, which was performed in 11-weeks old SPF-chickens by the recommended oral route, using one batch of AviPro AE at one maximum dose. The vaccine virus was able to spread horizontally from vaccinated to non-vaccinated chickens as 28 days post vaccination similar AE-specific antibody levels were detected in all vaccinated and contact chickens.

Thus, to prevent any negative influence of the product on non-vaccinated chickens, all animals in a population should be vaccinated.

The applicant did not perform any studies assessing spread to non-target species. According to scientific publications, AEV can naturally infect turkeys, pheasants, and pigeons. However, for the 30 years when the vaccine has been marketed and commercially used no spread to non-target species has been observed.

The applicant did not perform any studies assessing dissemination in the vaccinated animal. According to scientific publications, the Calnek 1143 strain is neurotropic and disseminated mainly in the nervous system of the chickens. AEV could be detected in alimentary tract and several internal organs such as liver, spleen, and pancreas.

One study on reversion to virulence of the attenuated virus was performed in 21 to 42-day-old SPF-chickens by the oral route, using the MSV at one maximum dose. No AEV could be detected after the second bird-to-bird passage onwards. Thus, the vaccine virus is safe in terms of reversion to virulence.

The intrinsic biological properties of the vaccine strain have been well characterised, both by scientific publications and by the data provided.

No specific studies were performed to examine recombination or reassortment of the included virus strain. As the virus RNA is not segmented, reassortment cannot occur. Homologous recombination is possible but over the 30 years the vaccine has been marketed and commercially used, there is no evidence that the natural cycling of vaccine strain resulted in the generation of virulent field strains.

The excipients used are classified as food additives and do not constitute a hazard. Based on this information, no 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.

The user safety has been adequately addressed and the warnings in the SPC are regarded as sufficient.

3.C. Clinical trials

AviPro AE proved to be safe in many field studies when administered as part of the standard vaccination program. More than 270,000 breeders of future broilers and layers have been vaccinated with AviPro AE without any safety concerns.

This is confirmed by the positive pharmacovigilance reporting of the period 2006 – 2020, summarized in the periodic safety update reports. Only low levels of either suspected adverse reactions or of suspected lack of expected efficacy were received.

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 all hazards identified have a negligible likelihood and therefore the estimation of the risk of these hazards is effectively zero.

Warnings and precautions regarding spread of the vaccine strain to unvaccinated chickens and other susceptible species as listed in the product literature are adequate to ensure safety to the environment when the product is used as directed.

3.E. Assessment required for veterinary medicinal products containing or consisting of genetically modified organisms

Not applicable.

4. EFFICACY DOCUMENTATION

4.A. General requirements

The clinical trials presented here intend to support the claims of efficacy for AviPro AE.

Most of the studies presented for this procedure were performed years ago and fulfilled the requirements of monograph 0588 at the respective time.

Studies that are currently no more required, were kept in the dossier for consistency.

Some of the requirements have changed since the studies were performed.

Most of the data was generated in field studies which were conducted years ago, according to the legislation valid at the time of performance of the study.

In most of the field studies, eggs were taken from vaccinated parent animals, and either embryos or hatched chicks were challenged under controlled laboratory conditions with a virulent AE strain to demonstrate the presence of passive immunity of the progeny.

Newer laboratory studies performed in 2012 and 2017 did not include any challenge infection anymore due to the 3R's approach, and the efficacy of the vaccine was demonstrated by serological examination of AEV antibodies only.

For most batches produced in the 1990s no documentation is available anymore at the Applicant's archive, but the applicant confirms that the batches used for the efficacy studies

were manufactured according to the description of the manufacture provided in Part 2 of this dossier.

The studies have been performed according to the respective EU-requirements valid at the time of testing since 1983.

- Directive 92/18/EEC, Part IV, B.3
- Directive 2001/82 as amended by Directive 2004/28/EC and updated Annex I to the Directive (2009/9/EC)
- Ph. Eur. Monographs 5.2.7. “Evaluation of Efficacy of Veterinary Vaccines and Immunosera”
- Ph. Eur. Monographs 0062 “Vaccines for Veterinary Use” and 0588 “Avian Infectious Encephalomyelitis Vaccine (live)”
- For most batches produced in the 1990s no documentation is available anymore at the Applicant’s archive, but the applicant confirms that the batches used for the efficacy studies were manufactured according to the description of the manufacture provided in Part 2 of this dossier.

The immunogenic properties were assessed for the following criteria:

- Intracerebral test infection for pullets
- Embryo susceptibility
- Serological examination of vaccinated animals at various intervals after vaccination
- Demonstration of maternally derived immunity of the progeny of layer and broiler breeders

The product is a live liquid vaccine for oral administration to chickens against clinical signs of Avian Encephalomyelitis (AE). The disease is caused by the Avian Encephalomyelitis virus a RNA Enterovirus from the family of Picornaviridae.

Clinical signs concern the neurological system and comprise of progressing ataxia and tremors of the head and neck. Clinical signs mostly occur in very young chicks and are only rarely seen in chicks between 3 and 7 weeks of age.

The active substance is strain Calnek 1143, isolated and described by Calnek in 1961.

Future layers and breeders are vaccinated once between 10th week of life and 4 weeks before the start of the laying period.

The onset of immunity in layers and breeder parents is 3 weeks after vaccination.

The duration of immunity in layers and breeder parents is at least 44 weeks after vaccination, analysed by serology.

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.

A study on the potency and safety of the MSV 1/83 was performed using 30 SPF chickens of 28 days of age. Animals were vaccinated with a dose of the MSV and challenged 21 days after vaccination with a virulent strain of AEV (van Roekel).

All vaccinated chickens remained healthy, all controls bird died, or showed clinical signs of AE, therefore MSV 1/83 was declared efficacious.

Study 2a/97 intended to determine the correct dilution of the van Roekel strain to carry out a conclusive challenge infection. However, it was not possible to induce clinical signs of AE in more than 70% of the chickens, therefore the study was not successful. It was concluded that this was due to the age of the chickens

(7 weeks), as the signs of disease rarely develop in older chicks.

A study intended to compare the serological response induced by a batch manufactured from the MSV 1/83 with the response induced by a batch manufactured from the new MSV 5020300 which is three passages away from the former MSV. 30 birds in 2 groups were vaccinated and blood samples taken before and 7, 14, 21, 28, 35 and 42 days after vaccination.

All animals were seronegative prior to the study. After D14 seroconversion was observed. At D42 after vaccination 93% of birds in Group 1 and 100% of birds in Group 2 were seropositive.

No significant difference in the serological response between both batches was observed and therefore an equal immunogenicity of both batches is assumed. This supports the onset of immunity within 3 weeks after vaccination.

A further studies' objective was to evaluate the potency of an AviPro AE vaccine batch with a novel EID_{50}-ELISA method measuring a serological response of vaccinated SPF chickens.

25 SPF chickens of the minimum age for vaccination (10 weeks) were used. 20 chickens were vaccinated with the minimum dose. 5 chickens were given placebo (water for injection). 3 and 6 weeks after vaccination blood samples were taken and analysed in the ELISA.

None of the birds died or showed clinical signs of the disease. At 3 weeks after vaccination all birds showed antibody titers for AEV above the test threshold.

6 weeks later the antibody titres further increased. All control birds remained negative.

The study demonstrates that a single oral vaccination with a titre determined in the ELISA test, which corresponds to the formerly registered minimum titer as determined in the hatch test lead to a seroconversion in all 20 birds at 3 weeks after vaccination increasing to 6 weeks after vaccination.

4.C. Clinical trials

Efficacy of vaccination was also demonstrated under field conditions in several controlled field trials.

A study was performed where chickens were vaccinated in the field to determine the potency of maternal immunity at the end of the laying period. To do so, the minimum efficacious dose of AviPro AE was administered via drinking water to 14 weeks old Lohmann Brown-chickens as part of the standard vaccination program. The chickens were observed for 8 weeks post vaccination.

No symptoms of local and systemic reactions that would originate from the vaccination by AviPro AE occurred during the entire observation period.

Serology of the breeder parents revealed that the vaccinates possessed circulating anti-AE-antibodies at 22 weeks of age.

The LB-progeny chickens hatched at the beginning of the laying period possessed maternal anti-AE-antibodies at first day of life and at 14 days of life.

The LB-progeny also did not develop clinical signs of AE even after challenge at 14 days of life. It is concluded that the oral application of a minimum dose of a batch of AviPro AE under field conditions can be considered efficacious for 14-weeks-old layer breeders and their progeny hatched at the beginning of the laying period.

A further study was performed to determine onset and duration of protection of broiler breeders in the field. In the study, four AviPro AE batches were compared in terms of safety and efficacy in a field trial on total of 22 500 chickens. The minimum dose of AviPro AE was administered via drinking water to 15 weeks old broiler breeders as part of the standard vaccination program. The chickens were observed for 9 months post vaccination.

No local or systemic reactions or AE symptoms have been observed regardless of the tested vaccine batch during the entire observation period.

It is concluded that the vaccine was efficacious in protecting chickens against AE since anti-AE antibodies were observed between 3 and 41 weeks after vaccination. Eggs laid 17 weeks after vaccination were used for an embryo susceptibility test. Eggs were inoculated with an embryo adapted AE strain. A low percentage of embryos showed virus specific alterations after inoculation the majority of the embryos was protected. The vaccine therefore complies with the test parameters.

Another study monitored the onset of protection after vaccination of layer and broiler parents.

Layer and broiler parents were applied the minimum dose per bird at 14 weeks (layers) and 12 weeks (broilers) of age.

Blood samples were drawn on D1 and D106 in layers and on D1, D83 and D95 in broilers and tested for anti-AE antibodies in the ELISA.

The level of maternal antibodies was high at 1st day of life. Serology of the vaccinates 8 days after vaccination in layers, did not show anti-AE antibodies. Serology in broilers after 20 days was positive.

A safety and potency study determined the onset of immunity and the passive immunity in embryos.

In this study, a minimum dose of AviPro AE was administered via drinking water to 75,470 broiler breeder parents at the age of 17 weeks as part of the standard vaccination program. The chickens were observed for 28 weeks (around 7 months) post vaccination.

19 days and 8 weeks p.v. blood samples of 10 chickens per flock were examined serologically for the presence of anti-AE antibodies.

Additionally an embryo susceptibility test was performed during the laying period at 28 weeks of life. Serological samples were positive between 19 days and 8 weeks after vaccination.

It is concluded, that the vaccine was efficacious as serological examinations were positive for anti-AE antibodies and the majority of embryos in the susceptibility test were protected.

Onset and duration of immunity were determined in a study, where a minimum dose of AviPro AE was administered via drinking water to 34,000 broiler breeder parents at the age of 14 weeks as part of the standard vaccination program. The chickens were observed for 9 months post vaccination.

Vaccinated chickens developed AE specific antibodies, detectable from 4 weeks post vaccination. The duration of immunity was determined up to 10 weeks post vaccination.

It is concluded that oral application of one dose of a batch of AviPro AE under field conditions as part of the standard vaccination program can be considered efficacious for 14-weeks-old broiler breeders.

An additional study on onset of immunity was performed where 77,000 broiler breeder parents were administered the minimum dose of AviPro AE via drinking water at 14 weeks of age. The chickens were observed for 10 months post vaccination.

Vaccinated chickens developed AE specific antibodies, detectable from 4 weeks post vaccination. The duration of immunity was determined up to 44 weeks post vaccination.

The applicant concludes that vaccination with AviPro AE was efficacious since all flocks examined serologically 4 and 44 weeks p.v. were positive for anti-AE antibodies.

Onset and duration of immunity, as well as passive immunity in embryos was analysed in a study where a minimum dose of AviPro AE was via drinking water broiler breeder parents at 14 weeks of age. The chickens were observed for 11 months post vaccination.

Vaccinated chickens developed AE specific antibodies, detectable from 5 weeks post vaccination. The duration of immunity was determined up to 41 weeks post vaccination.

In the embryo susceptibility test 14 weeks p.v. the majority of the embryos did not show virus specific alterations after inoculation of an embryo adapted AE strain.

It is concluded that, the administration of TAD AE vac was efficacious, since serological examination by ELISA revealed, that the vaccinates were positive for anti-AE antibodies between 4 and 41 weeks post vaccination and the majority of the progeny/flock was protected against infection with an embryo adapted strain via maternal antibodies.

In a supportive study from 1961 the incidence of egg and contact transmission and potency of maternal immunity was analysed

In this study, 10 MID (minimal infective dose)/chicken of the 5th embryo passage of AEV strain 1143 were administered via drinking water to 500 breeder parents at 11 months of age. Eggs were collected daily and hatched weekly, progeny was raised in isolation units.

Eggs for embryo susceptibility testing were collected pre-vaccination and at different intervals post-vaccination and challenged via the yolk sac with embryo adapted virus.

Furthermore, chicks were hatched from eggs laid at least 4 weeks post vaccination. These were challenged at one day of age via drinking water with strain 1143.

Embryo susceptibility tests following vaccination of breeders indicated that virus spread was rapid, immune eggs being determined as early as 2 weeks post vaccination. 4 weeks post vaccination a majority of the eggs were maternally immune. All day-old chicks from eggs laid 4 weeks post vaccination appeared to be immune to challenge via maternal antibodies.

Taking into account the cumulated data that was provided in the dossier, it can be concluded that the AviPro AE vaccine is sufficiently efficacious in the target species.

5. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The data submitted in the dossier demonstrate that when AviPro AE is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species chicken (future layers and breeding chickens) is favourable and the quality, safety of the product for user and the environment as well as efficacy of the product in the target species are acceptable.

POST-AUTHORISATION PROCEDURES

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC/labelling/package leaflet is/are available in the Union Product Database (UPD).

This section contains information on significant changes agreed after the original procedure, which are important for the quality, safety or efficacy of the product.

Sequence of significant variations

Classification code - Summary of change (Application number(s))	Approval date (end of procedure)
F.II.d.1.b Deletion of extraneous agents (EA) test on the finished product. **F.I.b.1.z** Deletion of EA test on the working seed. (DE/V/xxxx/WS/082 - DE/V/0292/001/WS/001)	08/09/2022
G.I.18 Alignment of the product information with version 9.0 of the QRD templates in accordance with Regulation (EU) 2019/6 (DE/V/0292/001/A/002)	12/08/2024