FRENCH AGENCY FOR VETERINARY MEDICINAL PRODUCTS

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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

French agency for food, environnemental and occupational health safety– French Agency for Veterinary Medicinal Products

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	FR/V/0245/001/DC
Name, strength and pharmaceutical form	Cevac IBird Lyophilisate for suspension for reconstitution in water
Applicant	CEVA- Phylaxia veterinary Biologicals Co. Ltd
Active substance(s)	Live Infectious Bronchitis Virus, strain 1/96
ATCvet code	QI01AD07
Target species	Chickens
Indication for use	For the active immunization of broiler chickens, and future layer chickens in order to reduce the impact on the ciliary activity and presence of virus in trachea resulting from the infection, which may be manifested in respiratory clinical signs caused by variant strains of infectious bronchitis virus belonging to the 793/B group

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 31 of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	29/05/2013

"This product was originally authorised under an EU procedure prior to 1st January 2021 where the UK participated as a Concerned Member State. Therefore, the contents of this Public Assessment Report are not owned by the Veterinary Medicines Directorate. Please contact the original Reference Member State for any queries in relation to this report."

Date product first authorised in the Reference Member State (MRP only)	29/05/2013
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, HU, IE, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK, UK

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests, which ensure the consistency of the product released on the market.

It has been shown that the product can be safely used in the target species; the reactions observed are indicated in the SPC.

The product is 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 product was demonstrated according to the claims made in the SPC.

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

II. QUALITY ASPECTS

A. Composition

Composition:

Active substance:

Live attenuated Avian Infectious Bronchitis virus, $10^{2.8}$ – $10^{4.3}$ EID_{50}/dose strain

1/96

List of excipients :

Gelatine
Hydroxypropylbetadex
Sucrose
Monosodium glutamate
Potassium dihydrogene phosphate
Dipotassium hydrogene phosphate
Purified water

The vaccine is filled in vials of hydrolytic glass type I presented in cardboard box with 1, 10 or 20 vials/box. The 500 doses presentation is filled in 3 mL vials. The 1000 doses presentation is filled in 3 mL or 10 mL vials. The 2500 and 5000 doses presentations are filled in 10 mL vials.

The

particulars of the containers and controls performed are provided and conform to the regulation of monographs 3.2.1 and 3.2.9 of the European Pharmacopoeia.

The choice of the vaccine strain, of the vaccine composition, of the dose volume and vaccination schedule are justified.

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

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. A corresponding manufacturing licence and GMP certificates are provided.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

The product is manufactured in accordance with the European Pharmacopoeia and relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with indicated pharmacopoeia monographs.

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 monographs.

The master and working seeds have been produced according to the Seed Lot System as described in the relevant guideline.

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

E. Control tests during production

The tests performed during production (candling, microbiological purity test, filled volume) are described in detail.

F. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements; any deviation from these requirements is justified. Relevant validations are provided.

The tests include in particular :

- appearance
- residual humidity
- virus identity
- virus titration
- purity
- Mycoplasma
- absence of extraneous agents according to Ph Eur 2.6.25

The demonstration of the batch to batch consistency is based on the results of 3 batches produced according to the method described in the dossier.

G. Stability

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (12 months) when stored under the approved conditions (2-8°C). According to the stability data, an overage in titre is performed to ensure the minimal guaranteed dose at the end of the shelf-life.

The in-use shelf-life (2h) of the reconstituted vaccine is supported by the data.

III. SAFETY ASSESSMENT

The vaccine is supplied in a multi-dose, lyophilized cake which is reconstituted by the end user for mass application through coarse spray or drinking water. Vaccination is recommended on broilers chickens from one day of age and for future layers from 10 days of age.

Safety studies have been performed with vaccine batches produced according the described production process.

Laboratory trials

The safety of the administration of one dose, an overdose and the repeated administration of one dose in the target animal is demonstrated in controlled laboratory studies which in total included 400 vaccinates and 292 control animals (SPF birds, commercial broilers and future layers). The investigation was performed according to the recommendations of Directive

2001/82/EC as amended and the relevant guidelines

The safety studies demonstrate that the administration of one dose, an overdose, and the repeated administration of a dose can be considered to be safe, when used in accordance with the recommended vaccination schedule. Some minor, transient adverse reactions were observed following vaccination (slight tracheal rales which may persist for at least 10 days).

Effects on laying performance were examined in a field trial in Hungary: 21000 layers were vaccinated with Cevac IBird at 11 and 101 days of age and compared with 42 000 controls vaccinated with other vaccines. The vaccination had no impact on the egg production rate.

Additional study has been conducted to demonstrate safety of the vaccination during lay period.

In laboratory conditions, 120 birds received twice maximal dose by oculo-nasal route 6 weeks apart during laying period. No adverse reactions, nor lesions in oviduct and no impact on egg production was evidenced.

These data were accepted and the statement that the repeated use of CEVAC IBird has been shown to be safe in layers during lay has been added in the SPC.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny therefore a specific study was not carried out.

A trial has been conducted in SPF chicks vaccinated at day old with 10 dose of CEVAC IBird vaccine mixed with 10 doses CEVAC Mass L administered by oculo-nasal route. No clinical signs nor lesions were observed, demonstrating safety of the mixed vaccination. Safety of the mixed vaccination has also been investigated in broilers and layers vaccinated at day old in the field. Reactions currently described in the SPC (slight tracheal rales or transient conjunctivitis) have not been observed after administration of mixed vaccines.

Mixing of 2 live infectious bronchitis strains increases the risk of recombination and possible emergence of new variants. This risk is presented in the SPC. It is also mentioned that the chance of a hazard occurring is very low.

The applicant has satisfactorily addressed special requirements to be taken into account for live vaccines:

- The vaccine virus disseminates to bursa, caecal tonsil, kidney, liver, lung, spleen, trachea and oviduct/testis. Rapid vaccine virus dissemination has been demonstrated by RT-PCR. Virus colonized most tissues tested, within 3 days of vaccination, and persisted in until the end of the study (28 days), the colonisation of the reproductive organs was less frequent.

- The vaccine strain is capable of horizontal transmission from vaccinated target animals to non-vaccinated target animals, following administration of an overdose to SPF animals. The spreading at least up to 28 days was demonstrated by PCR testing performed on bursa, caecal tonsil, kidney, liver, lung, spleen, trachea and oviduct/testis.No investigation of horizontal transmission under the recommended conditions of use was conducted in other species, in the absence of this data the SPC indicates that care should be taken to avoid spread to pheasants and turkeys.

-The conclusion of the reversion to virulence study, that the vaccine strain does not revert to a virulent form following 5 *in vivo* serial passages in groups of 7 SPF chicks, is acceptable.

- The risk of recombination between the vaccine strain and other IBV strains present in the field (field strains or vaccine strains) cannot be excluded and the probability to obtain a new virulent strain is not nil. Nevertheless, other vaccines containing the same type of IBV strain are already used in the field and until now no negative effects linked to these vaccines was observed.

Gentamicin sulphate and hydroxyproplybetadex present as excipients in the vaccine are not covered by the MRLs regulation. The gentamicin sulphate used during the production process is not recommended for use in chickens and is not listed in table I of the annex to regulation 37/2010 for chickens. As it is added only to the virus harvest and vaccinated birds ingest gentamicin below the MIC, it cannot be considered as pharmacologically active.

Hydroxyproplybetadex in the dose applied to the target species is not capable of any pharmacological activity, The use of low level of these components would have a negligible effect on the consumer safety. Furthermore the vaccine Cevac Transmune that contains also hydroxypropylbetadex as excipient is currently authorised in different Member States.

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

Field studies

The applicant has presented three field trials which were conducted in commercial farms in Hungary.

The first trial was performed in broiler chickens (20000 vaccinates and 22800 controls) vaccinated at one day of age by coarse spray.

Two other field trials were performed in future layers (total of 34680 vaccinates and 30480 controls) using a vaccination by drinking water. In one study the animals were vaccinated at 11 day of age and in the other study they received a repeated administration of vaccine at 11 and 101 days of age.

The results obtained reflected those observed in the laboratory safety studies, no adverse effects attributable to vaccination were observed and the parameters of animals vaccinated with Cevac IBird were not different to parameters of animals in the positive control group.

In additional trials, safety of the vaccination was demonstrated in 14400 commercial layer pullets vaccinated at day old and at 42 days of age with vaccine (standard vaccine batch) administered by spray and in 34000 layers vaccinated by spray during lay at 30 weeks of age and 56 weeks of age. No adverse reaction (clinical, lesions or egg production) was observed.

Ecotoxicity

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

The conclusions of the environmental risk assessment as presented by the applicant, that there is a very low risk to the environment associated with use of the vaccine, are accepted. The applicant has included the standard disposal statement for live vaccines on the product literature and this is considered acceptable.

IV. EFFICACY

The efficacy of the product has been demonstrated in laboratory challenge studies in accordance with the Ph.Eur. monograph 0442: Avian Infectious Bronchitis Vaccine (Live).

The efficacy on the target species chickens was demonstrated in SPF animals, broilers and future layers at the minimum age recommended for vaccination.

Minimum and standard doses were used in the efficacy studies.

Efficacy studies have been performed with vaccine batches produced according the described production process.

The challenge strain used in the efficacy studies is a 793/B strain which is a UK isolate corresponding to the second egg passage of a strain isolated from affected chickens in 1991 in Scotland.

Laboratory Trials

The efficacy studies provided in support of the claimed indications for Cevac IBird are supported by nine laboratory studies, which included either chickens vaccinated in laboratory conditions with the minimum dose ($10^{2.8}$ EID_{50}/dose in six studies), or chickens vaccinated in field conditions with standard batches ($10^{3.1}$ EID_{50}/dose in three studies). Challenge of study animals was conducted with a 793/B strain which is a UK isolate corresponding to the second egg passage of a strain isolated from affected chickens in 1991 in Scotland.

The animals used in the different challenge studies are SPF chickens (total of 57 vaccinates and 33 controls), broilers (total of 80 vaccinates and 75 controls) and future layers (total of 85 vaccinates and 70 controls).

The efficacy of the vaccine is demonstrated in SPF birds according to the requirements of the Ph. Eur. Monograph 0442, section 2.4.3.1. Immunogenicity – Ciliary activity of tracheal explants.

The efficacy in commercial chickens was demonstrated after a challenge performed either at 21 days or at 42 days after the vaccination. After the challenge, there was a significant reduction of the impact on ciliary activity of the infection induced by the challenge strain in the vaccinates compared to the controls. In two studies, a significant reduction of respiratory signs was observed in vaccinates by comparison with control animals.

The following claimed indications for Cevac IBird are considered to be supported by the nine laboratory studies:

For the active immunization of broiler chickens, and future layer chickens in order to reduce the impact on the ciliary activity of the infection, which may be manifested in respiratory clinical signs caused by variant strains of infectious bronchitis virus belonging to the 793/B group.

Onset of immunity is 3 weeks after one administration of the vaccine.

Duration of immunity is 6 weeks after the first vaccination.

New studies to recommend and investigate efficacy of spray vaccination were conducted in MDA-positive(*) future layers pullets.

(*) in the different efficacy studies MDA positive birds presented MDA titres between 6.3 log_2 and 7 log_2

	Groups	Challenge with virulent IB 793/B virus	Protection rate	Significant reduction in virus load in the trachea
Future layers	20 vaccinates (spray) 10 controls	3 weeks after vaccination	100% 20%	yes
Future layers	20 vaccinates (spray) 10 controls	6 weeks after vaccination	85% 0%	yes
Future layers	20 vaccinates (spray) 10 controls	9 weeks after vaccination	95% 20%	yes

Indication of protection as decrease of presence of the virus in trachea was accepted and added to current efficacy claims.

These studies allow to claim a 9 weeks duration of immunity for future layers vaccinated by spray.

Additional studies have been performed to assess compatibility of the mixed vaccination with CEVAC IBird and CEVAC Mass L in MDA-positive birds (*) vaccinated with both vaccines and subsequently challenged with virulent IB 7/93 strain.

(*) in the different efficacy studies MDA positive birds presented MDA titres between 6.3 log_2 and 7 log_2

	Groups	challenge	Total ciliary activity scores	Protection rate	Significant reduction in virus load in the trachea
Future layers	20 day old vaccinates (spray) 10 controls	3 weeks after vaccination	2.9/40 27.6/40	90% 20%	yes
Future layers	20 day old vaccinates (spray) 10 controls	6 weeks after vaccination	1.25/40 37.4/40	100% 0%	yes
Future layers	20 vaccinates (spray) 10 controls	9 weeks after vaccination	1.6/40 29.6/40	95% 20%	yes
broilers	20 vaccinates (spray) 10 controls	3 weeks after vaccination	2.4/40 39.3/40	100% 0%	yes
broilers	20 vaccinates (spray) 10 controls	6 weeks after vaccination	3.15/40 40/40	100% 0%	yes
broilers	20 vaccinates (spray) 10 controls	9 weeks after vaccination	0.1/40 26.7/40	100% 30%	yes

Efficacy of CEVAC Mass L in birds vaccinated with both vaccines and subsequently challenged with virulent Massachussetts IBV strain was also established.

All information related to the recommendation of mixing of the 2 vaccines has been put in the SPC.

Field studies

The applicant has presented three field trials which were conducted in commercial farms in Hungary.

The first trial was performed in broiler chickens (20000 vaccinates and 22800 controls) vaccinated at one day of age by coarse spray.

Two other field trials were performed in future layers (total of 34680 vaccinates and 30480 controls) using a vaccination by drinking water. In one study the animals were vaccinated at 11 day of age and in the other study they received a repeated administration of vaccine at 11 and 101 days of age. The animals were vaccinated with standard batches of vaccine ($10^{3.1}$ EID_{50}/dose).

Based on the daily monitoring of the flock health status and the serology monitoring there was no indication of an IBV field infection in these studies. Nevertheless 50 vaccinated and 60 control animals were taken from the field and were challenged in laboratory conditions. After the challenge, there was a significant reduction of the impact on ciliary activity of the infection induced by the challenge strain in the vaccinates compared to the controls.

Efficacy of the mixed vaccination was additionally investigated in broilers and commercial layers vaccinated at day old with both vaccinated administered by spray on the field and challenged 3 weeks later in laboratory with 793/3 virulent virus or Mass virus. 90% or 100 % protection was demonstrated in vaccinated birds.

V. 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 is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

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 is available on the veterinary Heads of Agencies website (http://www.hma.eu/vmriproductindex.html).

This section contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product. **Quality changes**

Summary of change	**Approval date**

Safety/efficacy changes

Summary of change	**Approval date**
inclusion of a compatibility statement with vaccine CEVAC MASS L (both vaccines can be mixed before administration).	2017
Vaccine is safe for administration to chickens during lay	2017
After vaccination by spraying, duration of immunity is 9 weeks	2017