Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION
PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Poulvac Bursine 2 lyophilisate for suspension for spray vaccination or for use in drinking water for chickens

Date Created: December 2015

PuAR correct as of 26/01/2018 when RMS was transferred to HU. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0462/001/MR
Name, strength and pharmaceutical form	Poulvac Bursine 2 lyophilisate for suspension for spray vaccination or for use in drinking water for chickens
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance(s)	Infectious bursal disease (IBD) virus strain Lukert: $10^{4.3}$ – $10^{5.5}$ $TCID_{50}$
ATC Vetcode	QI01AD09
Target species	Chickens (broilers and future layers/breeders)
Indication for use	For the active immunization of broilers, and future layers/breeders to reduce clinical signs caused by infectious bursal disease virus.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

(www.gov.uk/check-animal-medicine-licensed)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 32 (2) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	22nd July 2014
Date product first authorised in the Reference Member State (MRP only)	21st March 1994
Concerned Member States for original procedure	Bulgaria, Croatia, Hungary, Ireland, Slovenia, Romania

I. SCIENTIFIC OVERVIEW

This product was originally authorised for use in the UK in March 1994. It is recommended for the active immunisation of broilers, and future layers/breeders to reduce clinical signs caused by IBD. The product is a live attenuated vaccine containing the Lukert strain of the virus, and is administered to chickens from 7 to 28 days of age. A second vaccination should be administered 7 to 10 days after the first vaccination.

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, any reactions observed are indicated in the SPC[1]. 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[2] of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

II. QUALITY ASPECTS

II.A. Composition

The product contains the Lukert IBD virus strain at $10^{4.3}$ – $10^{5.5}$ $TCID_{50}$ and the excipients pharmatone, bacto-peptone, sucrose, N-Z amine type YT and glutamic acid sodium salt.

The container/closure system consists of hydrolytic Type I glass vials with a Type I rubber stopper, and the product is presented in 10 x 1000, 2500, 5000 and 10,000 doses. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the vaccine strain and the presence of preservative are justified.

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

II.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. The manufacturing method consists of the suitable preparation of pathogen free eggs, followed by addition of working seed virus. Eggs are appropriately incubated and the contents suitably prepared with the excipients. The product is bulk stored before being filled into vials and lyophilised.

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

II.C. Control of Starting Materials

The active substance is an established active substance substance not described in the European Pharmacopoeia (Ph. Eur), however, the processes used to create the virus are tested in line with Ph. Eur. guidance. The active substance is manufactured in accordance with the principles of good manufacturing practice. Starting materials of non-biological origin used in production comply with monographs in the Ph. Eur., and suitable certificates of suitability were provided in relation to the remaining biological products.

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

II.C.4. Substances of Biological Origin

The applicant provided a declaration of compliance with the Note for Guidance for Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01 Rev 2),

and the risk of TSE contamination associated with each of the starting materials of animal origin was assessed as follows:

IBD Virus, Lukert strain: Assessed as negligible risk.

SPF eggs: Avian origin, negligible risk.

Bactopeptone: Component of the stabiliser. Low risk.

NZ Amine YT: Component of the stabiliser. Derived from milk fit for human consumption. Other materials of porcine origin. Low risk.

Pharmatone: Component of the stabiliser. Low risk.

Tryptose phosphate broth: Component of the diluent for preparation of the seed inoculum. Derived from milk fit for human consumption. Other materials of porcine origin. Low risk.

Furthermore, the vaccine is administered to chickens which are not known to be susceptible to TSE agents. The risk of transmitting TSE infection by use of this vaccine is therefore considered to be negligible.

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Control tests performed during production include those for purity and bacterial contamination.

II.E. Control Tests on the Finished Product

The tests performed on the final product conform to the relevant requirements. The tests include in particular those for appearance, identification of the active substance, batch potency, sterility and purity, and the absence of extraneous agents. A series of tests for several common viral pathogens is also performed, along with appropriate physico-chemical tests and batch-to-batch consistency.

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. Other supportive data provided confirm the consistency of the production process.

II.F. Stability

Stability data on the finished product were provided in accordance with applicable European guidelines, demonstrating the stability of the product when stored under the approved conditions.

G. Other Information

Shelf-life as packaged for sale: 27 months
Shelf-life after reconstitution: 4 hours
Store and transport refrigerated (2°C – 8°C).
Protect from light.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose and an overdose in the target animal was demonstrated in a series of studies. The investigations were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines within the Ph. Eur.

No investigation of effect on reproductive performance was conducted because the vaccine is not intended for this category of animals. There are some data stating that this product might adversely affect the immune system of the vaccinated animal or its progeny. A suitable warning is contained within the SPC:

- Poulvac Bursine 2 produces increasing bursal damage on bird to bird passage and this is accompanied by a degree of immunosuppression.

Specific studies were carried out to describe the spread, dissemination, and reversion to virulence of the virus. No withdrawal period was required. The product may be used concurrently with Poulvac IB H120, but the product should not be mixed with any other vaccine or immunological product unless a suitable decision is made on a case-by-case basis.

Field studies

No field studies were provided or required. The product has been in use since the original authorisation with no unforeseen, adverse, safety-related issues.

Ecotoxicity

The applicant provided a Phase 1 environmental risk assessment in compliance with the relevant guideline which showed that no further assessment was required. The assessment concluded that there will be some positive dissemination of the product to other birds, but that spread will be localised within the immediate environment. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed:

- Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product was demonstrated in laboratory challenge studies, in accordance with the relevant requirements.

In a combined safety and efficacy study to establish minimum immunising dose, the product was diluted and provided to chickens at $10^{5.2}$, $10^{4.1}$, $10^{3.7}$ and $10^{3.2}$ $TCID_{50}$[3]. 20 chickens were vaccinated via drinking water, and 20 days after vaccination, all birds were tested for serum neutralising antibodies, with 5 birds from each dosage group then being necropsied and the bursa weighed. A negative control group was included in the study. On day 21, the remaining birds plus 20 controls were challenged by eye drop with pathogenic virus. 5 days later, all birds were necropsied and scored for bursal lesions and subjectively scored for bursal atrophy. Only 7% of negative control birds showed protection against bursal lesions, whereas protection was demonstrated in 60% of birds vaccinated at $10^{3.2}$, 93% of birds vaccinated at $10^{3.7}$, 87% of birds vaccinated at $10^{4.1}$ and 93% or birds vaccinated at $10^{5.2}$ $TCID_{50}$.

A further study was performed to establish the determination of efficacy of the product in young birds. Birds were provided with the minimum effective dose, $10^{4.3}$ $TCID_{50}$ by eye drop. Every three days, 10 birds from a total of 120 were then challenged with 100 CID_{50} of the CS88 strain of IBD virus. At necropsy, 54 hours later, the bursa was examined for relevant antigens. It was shown that resistance to challenge with IBD virus developed after 11 days following vaccination.

A third study examined the route of administration. 480 birds were inoculated with the product at $10^{4.3}$ $TCID_{50}$ per dose, by oral intubation. Birds were then divided into appropriate groups and challenged with 100 CID_{50} of strain CS88 by eye drop, or by oral intubation. Some of the birds were necropsied in order to examine bursal damage, while others were observed for 14 days for signs of IBD. A similar study then took place in which the proposed product was then administered by eye drop. From the results, it was established that at least 90% of birds were protected from IBD virus for both routes of administration of the product.

The effects of maternally derived antibodies (MDA) on the efficacy of the product were examined. 750 young birds with high levels of MDA to IBD were divided into groups and each group administered one of a variety of IBD vaccines, (the proposed product versus other commercially available products). Some birds were not treated, serving as negative controls. The virus content of the proposed product was $10^{5.4}$ $TCID_{50}$. There were 150 animals per group. 10 animals were taken from each group every 3 days and challenged by eye drop with 100 CID_{50} of CS88. At appropriate time points, animals were blood-sampled and tested for IBD antibodies, and sacrificed 54 hours after challenge in order to examine the bursa for IBD antigen. At this higher dose rate of the proposed product, it was

[3] $TCID_{50}$ – Median tissue culture infective dose.

shown that Poulvac Bursine 2 was most effective in protecting against IBD challenge. The proposed product had been applied by spray or intrabursally. The spray was seen to be more effective.

In a further study, the determination of the efficacy of a single sprayed vaccination of the proposed product in high and low MDA chickens was analysed. Approximately 500 birds from high and low MDA flocks were sourced. The proposed product was compared to a positive control product, and a third group were not vaccinated. The product was applied by spray at $10^{4.3}$ $TCID_{50}$. 10 chickens from each group were challenged by eye drop with 100 CID_{50} CS88. Necropsies occurred 54 hours later, and the bursae were examined for IBD antigen. Blood samples were taken at appropriate time points in order to establish the presence of IBD antibodies. A certain number of animals from each group were retained and challenged at day 42. They were observed for clinical signs of IBD. From results, it was shown that a single spray of the product to low MDA birds resulted in a delayed immune reaction. Although complete protection was observed after day 27. In the high MDA group, complete protection from clinical signs and mortality occurred but infection of the bursa was comparable to that of unvaccinated animals. It was therefore shown that high titres of MDA affect the efficacy of the product, although some resistance to clinical signs and mortality was also noted.

Another study examined 3 IBD vaccines, including the proposed product, (titre not indicated), given via the drinking water to MDA positive or negative chickens. 3 weeks after vaccination, vaccinated animals and non-vaccinated controls were challenged with virus. Following this all animals were necropsied and examined for IBD lesions. The product was shown to offer a high degree of protection to IBD.

A comparison was made of the proposed product and available products, when given by drinking water to young birds exhibiting MDA to IBD. Chickens were vaccinated at various time points and 4 weeks after vaccination the challenge virus was administered by eye drop. 4 days after challenge, the birds were necropsied and examined for signs of bursal disease. Although the titre of the proposed product was not described, it was noted that the efficacy of the proposed product increased once MDA levels decreased. Because of the interference of maternal antibody, the product is recommended for use as a repeat vaccination. Refer to the SPC for detail.

Field Trials

Field trials indicated that maternal antibody levels, rearing and management conditions, age of birds and severe incidence of IBD had an effect on the efficacy of the product. These data are all reflected within the SPC.

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 benefit/risk profile of the product(s) is favourable.

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 Product Information Database of the Veterinary Medicines Directorate website.

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The post-authorisation assessment (PAA) 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.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

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