ANNEX I

THE NAMES, PHARMACEUTICAL FORM, STRENGTH OF THE VETERINARY MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTE OF ADMINISTRATION, RECOMMENDED DOSE, WITHDRAWAL PERIOD, APPLICANT/MARKETING AUTHORISATION HOLDER IN THE MEMBER STATES

Member State	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration	Recommended dose	Withdrawal period (meat)
Belgium	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Bulgaria	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Czech Republic	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Denmark	Fort Dodge Animal Health	Poulvac Bursa	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Estonia	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Spain	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Germany	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Greece	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Hungary	Fort Dodge Animal Health	Poulvac Bursa Plus vakcina A.U.V.	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days

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Italy	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Latvia	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Lithuania	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
The Netherlands	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Poland	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Portugal	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Romania	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Slovakia	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days
Slovenia	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days

Member State	Applicant/ Marketing Authorisation Holder	Invented name	Pharmaceutical form	Strength	Animal species	Route of administration	Recommended dose	Withdrawal period (meat)
United Kingdom	Fort Dodge Animal Health	Poulvac Bursa Plus	lyophilisate for suspension in drinking water	Live Infectious Bursal Disease virus, strain V877 – $10^{2.2}$–$10^{3.4}$ EID_{50} per dose	Chickens from 10 days of age	For oral administration in drinking water	One dose from 10 days of age	Zero days

ANNEX II

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF POULVAC BURSA PLUS

1. Introduction

Poulvac Bursa Plus is a live vaccine against Infectious Bursal Disease Virus (IBDV), also known as Gumboro disease. Given its residual pathogenicity, the vaccine strain, V877, is classified as "intermediate plus" and also known as a "hot" strain.

The vaccine is indicated for the active immunisation of chickens with maternal antibody levels of ≤ 500 ELISA units, to reduce mortality and bursal lesions of Gumboro disease.

The vaccine is to be specifically used in case of outbreaks caused by very virulent IBDV (vvIBDV) strains.

Such very virulent field strains have occurred since the late 1980's in Europe[1,2]. Until the emergence of those strains the common practice in broiler production was to vaccinate hens just before laying in order to induce a high level of passive immunity in the chicks which could protect them up to an age when infection by IBDV was less detrimental with regards to immunosuppression. At that time, because the hypervirulent strains were able to breakthrough high maternally derived antibodies (MDA) levels, live vaccination of broilers became necessary.

The potential advantage of using "intermediate plus" or "hot" strains, such as the one contained in Poulvac Bursa Plus is that they could break through higher maternally derived antibodies (MDA) levels than milder strains can do. However, one of the problems to assess the efficacy of vaccination in commercial broilers (with MDA) under laboratory conditions is that they are usually not clinically affected by a vvIBDV challenge, as Specific Pathogen Free (SPF) chickens are. Layer chicks are clinically more sensitive than broilers[2].

For Poulvac Bursa Plus, the optimum day of vaccination recommended in the Summary of Product Characteristics (SPC) needs to be calculated using the Kouwenhoven's formula; the target maximum MDA levels at the time of vaccination is 500 ELISA Units using a commercially available kit, but whatever the vaccination day calculation reaches, it is contra-indicated to vaccinate chickens less than 10 days of age.

During the mutual recognition procedure concerns were raised by Belgium that the benefit/risk balance of Poulvac Bursa Plus might be considered unfavourable. Belgium argued that the study conducted by the Applicant according to Ph. Eur. monograph 01/2008:0587 showed that this vaccine strain causes significant damages to the Bursa of Fabricius, which in turn result in immunosuppression. In addition the intrinsic immunosuppressive nature of the vaccine strain is further evidenced in another study. It was considered that the risks associated with this immunosuppression were not sufficiently addressed in the application.

2. Assessment of Poulvac Bursa Plus

2.1. Safety

The Marketing Authorisation Holder (MAH) provided 5 pivotal studies, 7 supportive studies and 3 field studies in order to assess safety of the vaccine.

Maximum doses of virus, at minimum passage level, were used in almost all the pivotal safety studies (4 out of 5). Although the oral route is recommended, some safety studies have been carried out using the intraocular route. This allows the accurate dosing of the virus which, the MAH states, is not possible in very young birds by the oral route.

[1] Chettle N., Stuart J. C., Wyeth P. J. 1989. Outbreak of virulent infectious bursal disease in East Anglia. Veterinary Record, 125:271–272.

[2] Van den Berg T. P., Gonze M., Meulemans G. 1991. Acute infectious bursal disease in poultry: Isolation and characterization of a highly virulent strain. Avian Pathology, 20:133–143.

From the studies that were presented in the safety part of the dossier, the following conclusions can be drawn:

- When administered to SPF chickens using a 10 times overdose, the vaccine does not cause clinical signs or mortality. Although the Ph. Eur. monograph 01/2008:0587 is not directly applicable, the vaccine strain was shown to be compliant with its section 2.4.1 "safety".

- The vaccine does not comply with the Ph. Eur. monograph concerning the section 2.4.2 since higher than acceptable damage to the bursa of Fabricius was observed. However, the monograph is only intended for classical strains and bursal damage is expected to be associated with intermediate plus vaccine strains. This is an acceptable risk associated with the protection provided against vvIBD in the face of MDA.

- A study to assess the potential immunosuppression linked to administration of the vaccine was carried out according to the recommendations of the Ph. Eur. (using SPF chickens). The results showed that the vaccine strain notably reduced the serological response induced by vaccination against Newcastle Disease Virus (NDV) observed in chickens previously vaccinated using Poulvac Bursa Plus. This reduced serological response against NDV was however not translated into a reduction of the clinical protection against a virulent challenge.

- With respect to the level of bursal damage seen in SPF birds vaccinated with Poulvac Bursa Plus it is noted that the results of independent confirmatory testing of Poulvac Bursa Plus conducted by Germany and presented during the current procedure indicate that the level of bursal lesions seen are in line with those seen following vaccination with similar products which are already authorised in many Member States and therefore used widely within the European Union.

- The vaccine strain is able to spread to incontact chickens, but is very unlikely to increase in virulence.

- There is no risk for the consumer of vaccinated chickens, nor is there any risk for the user of the vaccine or the environment.

- The field study supports the safety of the vaccine.

- Since the product has been authorised, the reported incidence of adverse reactions is zero which indicates that the safety profile is acceptable.

- The SPC reflects the results of the various safety studies.

- Product Safety Update Reports in the UK, where the product has been authorised since 1998, have not indicated a problem with immunosuppression.

- Although no compatibility is claimed, serological data have been provided to support an absence of a negative interaction between Poulvac Bursa Plus and other vaccines. In view of the fact that no compatibility statement is claimed it is considered that sufficient information has been provided to support an absence of a negative interaction between Poulvac Bursa Plus and other vaccines.

- These types of product are for use in specific cases where there is evidence of vvIBD and where the level of bursal damage incurred is a necessary risk to achieve the protection provided against vvIBD. The risk of bursal damage and limited immunosuppression are clearly stated on the SPC (as is the need to restrict the use of the product to case of outbreaks of very virulent IBDV strains) and form part of the risk benefit assessment conducted by the veterinarian when deciding to use this product.

2.2. Efficacy

The MAH provided 2 pivotal studies, 7 supportive studies and 4 field studies. Efficacy studies have been carried out both under laboratory conditions, in SPF and commercial chickens with MDA, and under field conditions.

From the studies that were provided in the efficacy part of the dossier, the following conclusions can be drawn:

- Efficacy of the vaccine (minimum titre) has been shown using SPF chickens of the minimum age recommended: reduction of the bursal lesions and prevention of the mortality caused by a vvIBDV was achieved in those animals. An onset and duration of protection of respectively 14 and 32 days have been demonstrated.

- Efficacy of the vaccine in the presence of a range of MDA titres (mean titre of around 500 ELISA Units as recommended) was also shown under laboratory conditions: significant reduction of the bursal lesions was shown at 14 and 32 days post challenge. A detailed analysis of the data provided concluded that Poulvac Bursa Plus is able to overcome Infectious Bursal Disease ELISA titres of ≥ 500.

- Poulvac Bursa Plus has a negative impact on the serological response induced by vaccination against NDV. However, this effect did not affect the ability of the Newcastle Disease vaccine to protect against challenge with virulent NDV. The effect on serology is adequately reflected in the SPC.

- Under field conditions it was shown that Poulvac Bursa Plus was able to restore performance lost due to vvIBD which had broken through the protection provided by classical vaccines containing mild or intermediate strains. These benefits have been shown in the field in circumstances where the product is intended to be used and in the face of MDA levels which must necessarily be considered typical.

2.3. Benefit/Risk assessment

Benefits

Under laboratory conditions, efficacy against vvIBDV was shown using SPF chickens. Prevention of mortality and reduction of bursal lesions were demonstrated. An onset and duration of protection of respectively 14 and 32 days were demonstrated.

The onset and duration of immunity has been confirmed in commercial broiler chicks in a similar laboratory study in the presence of MDA.

Field data confirm the benefits of vaccination under practical conditions on sites which have experienced ongoing problems with vvIBD where intermediate products have not been successful at controlling the vvIBD problem. These have been under practical conditions, in flocks with levels of MDA which necessarily should be considered typical of situations where the product would be used.

The breakthrough titre has been supported, which underpins the proposed recommendation for use and confirms the ability of the product to be used to overcome MDA (present at levels as specified in the SPC), an issue which typically causes problems for intermediate vaccines.

Risks

There are no risks for the user, the consumer or the environment.

The vaccine has a negative effect on the level of the serological response to NDV vaccination, however there was no affect on the ability of NDV vaccine to induce a protective response capable of resisting challenge with virulent NDV.

The level of bursal lesions seen in independent confirmatory testing of Poulvac Bursa Plus is in line with those seen following vaccination with similar products which are already authorised in several Member States and used within the EU.

Benefit/risk balance

Efficacy of the vaccine has been adequately demonstrated in the laboratory, sufficient to confirm prevention of mortality and reduction of bursal lesions caused by vvIBDV using SPF chickens. The onset and duration of immunity has also been confirmed in commercial broiler chicks in a similar laboratory study in the presence of MDA levels as specified in the SPC. There is no requirement to demonstrate better protection than existing products, nevertheless it has been shown under field conditions that Poulvac Bursa Plus is able to restore performance lost due to vvIBD which has broken through the protection provided by classical vaccines containing mild or intermediate strains. These benefits have been shown in the field in circumstances where the product is intended to be used and in the face of MDA levels which must necessarily be considered typical. Therefore, the benefits of the product have been adequately demonstrated and that any risks associated with residual virulence is a recognised risk associated with this type of product, which is only recommended for use in an environment contaminated with vvIBD. There are sufficient recommendations and warnings provided to ensure that the veterinarian can determine whether the product is appropriate for use in an outbreak of vvIBD.

The benefit/risk balance for the product is considered positive.

GROUNDS FOR RECOMMENDATION OF THE GRANTING OF MARKETING AUTHORISATIONS

Having considered all the overall submitted data in writing the CVMP concluded that:

- Although the product did not comply with Ph. Eur. monograph (01/2008:0587) for classical IBDV vaccines, in that there was bursal damage and an interference on the serological response to NDV, it was acknowledged that there was no requirement to comply with this monograph because the product was classified as an intermediate plus strain.
- It was accepted that the immunosuppression seen was an acknowledged risk associated with the product, which was offset against the demonstrated ability to provide protection against vvIBD in the face of MDA levels as specified in the SPC.
- The SPC provides adequate information to the end user to enable the appropriate use of the product, including a recommendation to only use the product where vvIBD was present.
- The safety and efficacy data provided by the applicant were sufficient to consider that the overall benefit-risk balance for the product is positive.

Therefore, the CVMP recommended the granting of the Marketing Authorisations for Poulvac Bursa Plus for which the Summary of Product Characteristics, Labelling and Package Leaflet set out in Annex III of the CVMP Opinion.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

The valid Summary of Product Characteristics, Labelling and Package Leaflet are the final versions achieved during the Coordination group procedure.