Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
Woodham Lane
New Haw
Addlestone
Surrey KT15 3LS

MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Poulvac IB H120

PuAR correct as of 10/10/2017 when RMS was transferred to DE. Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0463/001/MR
Name, strength and pharmaceutical form	Poulvac IB H120
Applicant	Zoetis UK Limited 5th Floor, 6 St. Andrew Street London EC4A 3AE
Active substance(s)	Live, attenuated Avian Infectious Bronchitis Virus Strain H120: $10^{3.0}$ – $10^{4.9}$ EID_{50}
ATC Vetcode	QI01AD07
Target species	Chickens
Indication for use	For the active immunisation of chickens in order to reduce the detrimental effect on the ciliary activity resulting from infection with Infectious Bronchitis virus serotype Massachusetts, which is related to the development of respiratory clinical signs. Onset of immunity: 25 days Duration of immunity: 16 weeks

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Mutual recognition application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	23rd October 2013
Date product first authorised in the Reference Member State (MRP only)	1981
Concerned Member States for original procedure	Belgium, Bulgaria, France, Germany, Italy, The Netherlands, Romania, Spain

I. SCIENTIFIC OVERVIEW

Poulvac IB H120 was first authorised in the UK in 1981 and reviewed in 2005 in line with new EU Directive. It has now undergone a Mutual Recognition procedure. The product is a live, attenuated vaccine against avian infectious bronchitis virus (IBV) for use in chickens. The product is a lyophilised powder formulation containing $10^{3.0}$ – $10^{4.9}$ EID_{50} IBV strain H120 per dose following reconstitution. The vaccine is administered via eye drop, drinking water or by coarse spray.

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 slight 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 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.

II. QUALITY ASPECTS

A. Composition

[1] SPC – Summary of Product Characteristics

The product contains live, attenuated Avian IBV strain H120 as the active and D-mannitol, gelatin, myo-inositol and casein enzymatic hydrolysate as the excipients.

The container/closure system consists of hydrolytic Type I glass vials, closed with Type I butyl rubber elastomer stoppers and aluminium overseal. Vials contain either 1000, 2500, 5000 or 10000 doses and are packaged in cartons of 1 or 10 vials. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the vaccine strain is 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. The product is manufactured by first inoculating and incubating SPF eggs with a seed suspension prepared from the Working Seed Virus (WSV). Following incubation healthy eggs are cooled, disinfected and the virus is harvested. The virus is stabilised and frozen. Virus suspensions are thawed and filled into sterilised vials before lyophilisation is performed under vacuum. Finally stoppers are inserted and the vials sealed with aluminium caps. Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is Avian IBV strain H120, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice. 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 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 are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

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. The tests include in particular

visual inspection, batch potency, residual humidity, microbial purity and relevant tests for extraneous agents.
The demonstration of the batch to batch consistency is based on the results of seven batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

G. Stability

Stability data on the antigen has been provided in accordance with applicable European guidelines, demonstrating the stability of the antigen when stored at -50°C for up to 24 months.

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 when stored under the approved conditions. Data were provided for batches stored at 2-8°C for 36 months. A shelf life of 2 years is supported.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided. Vaccine vials were reconstituted using water at 30 °C and incubated for up to 4 hours, supporting the proposed shelf life of 4 hours.

H. Genetically Modified Organisms

Not applicable.

J. Other Information

- The shelf life of the finished product as packaged for sale is 2 years.
- The shelf life after dilution or reconstitution according to directions is 4 hours.
- Store and transport refrigerated (2 - 8°C).
- Protect from light.
- Do not freeze.

III. SAFETY ASSESSMENT

Laboratory trials

The safety of the administration of one dose and an overdose in the target animal is demonstrated. Supportive studies were submitted to demonstrate the safety of the product following a single administration to chickens. The studies were only supportive in nature but indicate the product is safe to use following administration of a single dose.

A study was provided that investigated the effect of a single administration of an overdose in chickens. Each bird received at least a 10-fold overdose and no significant adverse reactions were observed. A similar study using day old chicks was also submitted, which again showed the safety of the vaccine following overdose.

The applicant has not submitted studies to specifically demonstrate the safety of repeated doses. This was not considered necessary as the vaccine is indicated for single administration to chickens only. However the applicant has summarised published literature on repeated administration of the product. In one study from the literature birds received two vaccinations three weeks apart and no adverse reactions were observed. This suggests repeat administration of the product is safe.

Effects on reproductive performance were examined. In the first study submitted vaccination was administered via coarse spray to day old chicks and indicated no damage is caused to the oviduct. In the second study chickens were vaccinated during lay. The results demonstrate that the product is safe to use during lay. However the following warnings have been included on the SPC and product literature:

- Can be used before the onset of lay in chickens intended for breeding.
- Do not use in birds in lay and within 4 weeks before the onset of the laying period.

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.

Specific studies were carried out to describe the spread, reversion to virulence and biological properties. The studies demonstrated that the vaccine can spread from vaccinated to unvaccinated in-contact birds and cause seroconversion. Specific studies were not submitted to look at dissemination as this is only essential for zoonotic diseases. No evidence of the dissemination has been seen for the vaccine in any of the other studies. Reversion to virulence was investigated and no evidence was seen following serial passage through chicks. No additional test on the biological properties were necessary and whilst there is the possibility of recombination between IB virus strains, no evidence has been identified of any new strain derived from recombination during the long history of use of the vaccine. Therefore the risk of recombination is considered to be low. Appropriate warnings are included in the SPC:

- The vaccine virus spread from vaccinated to non-vaccinated chickens. Care should be taken in the planning and implementation of vaccination programmes and it is recommended that all chickens on a site be vaccinated with this product.

The active substance is of biological origin and all excipients are normal substances that do not require an MRL. Based on this information, a zero days withdrawal period is proposed.

There are no claims that the product is recommended for use with any other products. However additional studies were provided to demonstrate the safety of the vaccine when used with other Poulvac products; Poulvac NDW and Poulvac IB primer. These studies are only supportive in nature but no adverse reactions were observed following the administration of this vaccine with the other Poulvac products. The following warning has been included in the SPC:

- No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use

this vaccine before or after any other veterinary medicinal product therefore needs to be made on a case by case basis.

Field studies

To support the field safety of the vaccine PSURs were provided covering the period from 1999 to 2011. No suspected adverse reactions were reported during this period which supports the safety of the vaccine's use in the field.

Four field trials were also provided. The studies demonstrated the safety of the vaccine when used in birds in lay as described above. It was also observed that on farms where there were confirmed IBV problems vaccination improved performance and no adverse reactions were observed. The Production Index (calculated based on daily growth, food conversion and mortality) was compared for previous non-vaccinated flocks and the vaccinated flocks. The Production Index was seen to improve on all farms following vaccination and the vaccine was indicated to be safe for use in the field.

Ecotoxicity

The applicant provided a Phase I environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that whilst this is a live vaccine that is excreted by vaccinated birds it does not revert to virulence. The product has been used for many years without reported problems and due to the nature of the product it is not expected to cause any ecotoxic effects. It was concluded that the risk to the environment is minimal. Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

Clinical Studies

Laboratory Trials

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements. In the studies that were submitted efficacy was demonstrated by using challenge with Massachusetts strain M41.

Onset of Immunity
Studies were provided that investigated the onset of immunity. In the study day old chicks were vaccinated with Poulvac IB H120. The chickens were divided into 6 groups of 25 animals with 1 group of 10 acting as control and receiving no vaccination. Each of the 6 groups of chickens received vaccination with the test product administered via the ocular/nasal route, coarse spray or oral administration. All chickens were then challenged 25 days after vaccination by the intratracheal route.

Blood samples were collected before vaccination and 24 hours after vaccination for serology. Five days after challenge post mortem was carried out and the Cilia

Stopping test (CST)[2] was used to determine protection from the vaccine. The results demonstrated that the control animals all had complete cessation of ciliary function. Meanwhile the vaccinated birds had an increase of virus neutralising antibodies detected by serology and only a small loss of ciliary function was observed in a few cases. Onset of immunity was established as 25 days.

A supportive study that investigated the maternally-derived immunity was also submitted. Chicks with maternally derived antibodies (MDA) were vaccinated with Poulvac IB H120 and challenged 27 days later. The results of the study demonstrated the vaccine offered protection against challenge and support the efficacy of the vaccine in MDA-positive birds.

Duration of Immunity

Studies that investigated the duration of immunity were also supplied. In one such study day old chicks were divided into a control and test group. The 20 chicks in the control group were not vaccinated whilst the 25 chicks in the test group received the vaccine administered via the ocular/nasal route. All of the chicks in the test group and 9 of the controls were challenged 49 days post-vaccination. Blood samples were taken before vaccination, then 28 days and 48 days after vaccination for serology. Birds were euthanized and the trachea removed for analysis by the CST 5 days after challenge. The results of the serology demonstrated an increase in virus neutralising antibodies following vaccination. CST showed vaccinated birds retained ciliary function, 89% compared with 0% of the control animals, after challenge. This study indicates birds are protected against IB challenge up to 49 days after vaccination.

In a similar study 145 day old chicks were divided into 7 groups. Group 1 contained 10 birds which were unvaccinated and used to determine MDA levels. Group 2 contained 10 unvaccinated birds, whilst Groups 3 and 4 had 25 unvaccinated birds. Groups 5, 6 and 7 each contained 25 birds that received the vaccine via the ocular/nasal administration route. Chicks in Groups 2 and 5 were challenged 16 weeks after vaccination. Group 3 and group 6 received a booster vaccination with Poulvac i-Penta instead, whilst no challenge or booster was administered to Groups 4 and 7 at 16 weeks post-vaccination.

Blood samples were collected from Group 1 on day 1 and blood was taken from vaccinated and control birds 3, 9, 16, 19 and 21 weeks post-vaccination. Serology was performed and 6 days after challenge birds from Groups 2 and 5 were euthanized and tracheas removed for CST. Serology demonstrated an increase in virus neutralising antibodies following vaccination. Higher titres against IB antigens was seen following booster vaccination with Poulvac i-Penta, indicating Poulvac IB H120 can act as a primer. The CST analysis showed unvaccinated birds had reduced cilia movement (0% protected) whilst cilia movement was maintained in 91% of vaccinated birds. The study demonstrates a duration of immunity of 16 weeks following vaccination with Poulvac IB H120.

[2] CST – Ciliary stopping test. Tracheal explants are used to evaluate ciliary activity; normal, incomplete cessation and complete cessation of movement. A % protection can be determined from the number of birds where no movement is detected compared with the number where movement is detected.

Additional supportive studies were supplied also demonstrating protection from challenge up to 16 weeks after vaccination. The duration of immunity of 16 weeks for Poulvac IB H120 has been established.

Minimum Immunising Dose

A study was provided to support the minimum immunising dose. Day old chicks were divided into groups and received different titres of the vaccine. All groups contained 25 birds, apart from Group 4 which had 24, and received vaccination via the ocular/nasal route. Group 1 received a vaccine dose of 1.5 $\log_{10}EID_{50}$, Group 2 received 2.0 $\log_{10}EID_{50}$, Group 3 received 2.5 $\log_{10}EID_{50}$/dose and Group 4 were given 3.0 $\log_{10}EID_{50}$/dose. Group 5 remained unvaccinated and acted as the control. All birds were challenged 21 days post-vaccination. Blood samples were taken before and 21 days after vaccination for serology. Six days after challenge birds were euthanized and tracheas removed for CST.

The results showed an increase in virus neutralising antibodies following vaccination. After challenge the number of birds with cilia movement was counted per group and the percentage protected was calculated. The results showed that no cilia movement was seen in control birds but in birds vaccinated with the highest dose cilia movement was identified in all but 1 bird. Group 1 was 14% protected, Group 2 was 22% protected and Group 3 was 12% protected. Group 4, which received the maximum vaccine dose in this study, were 98% protected. Therefore it was determined that the minimum immunising dose of Poulvac IB H120 is $10^{3.0}$ EID_{50}.

Field Trials

No field trials have been submitted. Instead PSURs have been submitted covering the period 1999-2011 and during this time no lack of efficacy reports were submitted. It is accepted that the efficacy of the vaccine is confirmed.

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 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 Product Information Database of the Veterinary Medicines Directorate website.

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

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.

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