Agencia Española de Medicamentos y Productos Sanitarios

C/Campezo 1, Edificio 8
28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

FINAL PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Nobilis SE Live

"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."

MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0282/001/DC
Name, strength and pharmaceutical form	Nobilis SE live lyophilisate for use in drinking water for chickens
Applicant	Intervet International B.V. Wim de Körverstraat 35 Boxmeer 5831 AN The Netherlands
Active substance(s)	Live, attenuated *Salmonella enterica* subsp. *enterica* serovar Enteritidis strain CAL10 Sm+/Rif+/Ssq- 1-6 x 10^8 CFU* *CFU: Colony Forming Unit
ATC Vet code	QI01AE01
Target species	Chickens (future layers and breeders)
Indication for use	Chickens (future layers and breeders): Active immunisation to reduce colonisation of internal organs and faecal excretion of *Salmonella* Enteritidis field strains. Onset of immunity: 14 days after the first vaccination and 4 weeks after the third vaccination Duration of immunity: 60 weeks after completion of the recommended three vaccination schedule

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies website (http://www.hma.eu).

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MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	Day 210: 28/02/2018
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	AT, BE, CY, CZ, DE, EE, EL, FR, HR, HU, IT, LT, LU, LV, MT, NL, PL, PT, RO, SI, SK and 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 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. Qualitative and quantitative particulars

The product contains live attenuated *Salmonella enterica* subsp. *enterica* serovar Enteritidis strain CAL10 Sm+/Rif+/Ssq-, 1-6x10^8 CFU/dose and excipients (skimmed milk, sucrose, gelatin and HEPES buffer.)

The container/closure system is colourless glass bottles of hydrolytic glass type closed with bromobutyl rubber stoppers and sealed with aluminium caps.
The choice of the vaccine strain, formulation and absence of preservative 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.

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

C. Control of Starting Materials

The active substance is live attenuated *Salmonella enterica* subsp. *enterica* serovar Enteritidis strain CAL10 Sm+/Rif+/Ssq-, an established substance described in the European Pharmacopoeia. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specifications have been provided.

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

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; any deviation was adequately justified.

The master and working seeds have been produced according to the Seed Lot System as

described in the relevant guideline.

D. Control tests during production

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

E. 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 appearance, vacuum, identity tests (morphology, serology, biochemical tests, presence of markers), bacterial count, purity test and residual moisture.

The demonstration of the batch to batch consistency is based on the results of 4 batches produced according to the method described in the dossier. Other supportive data provided confirm the consistency of the production process.

F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions.

The in-use shelf-life of the reconstituted vaccine is supported by the data provided.

G. Other Information

None.

III. SAFETY ASSESSMENT

The used batches of the vaccine contain the antigen maximum dose.

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 two studies:
-One study about general safety with vaccination of SPF chickens with one dose and overdose of the vaccine and revaccination, and after observation until 28 days of age. --
And the second study with vaccination of commercial breeders according the vaccination scheme in a total of 4 administrations of vaccine.

The investigation was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The conclusion is that the vaccine has been demonstrated the safety in the target specie after the repeated administration.

Effects on reproductive performance were examined: the vaccine is safe after the vaccination in future layers and breeders according the schedule of vaccination, but a recommendation is set in the texts, as do not use within 3 weeks before the onset of lay and during the laying period.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny. A study of different immunological responses after the vaccination has been performed, and the results were that no negative influence by the vaccine had been observed.

Specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the live vaccine strain. After the first vaccination, the vaccine strain colonized liver, spleen and caecum of vaccinated birds for a 3-4 weeks period and it is shed to unvaccinated animals for a 3 weeks period. The level and duration of spread and internal organ colonization of the vaccine strain decreases with subsequent vaccinations. Unvaccinated animals results immunized against *Salmonella* through shed of vaccinated animals.

The vaccine strain is only detected in cloacae samples, but not in litter analysis, when animals are vaccinated with an overdose and as a maximum is detected during 3 weeks after the first vaccination.
Data from the studies support the absence of Salmonella on the litter after the vaccination of the birds in any case after 21 days of vaccination. Moreover, the vaccine strain is not excreted to the environment at 28 days after the first vaccination. The vaccine strain does not revert to virulence after 5 passages in birds.

The excipients used (no preservatives and adjuvants), are out of the scope of the MRL regulation. But a withdrawal period is proposed taking into account the zoonotic risk associated with the vaccine strain and in line with the previous studies.

The interaction of the vaccine with the simultaneous use of other medicinal products has been studied. The conclusions are that the vaccine strain is highly sensitive to chemotherapeutics as quinolone antibiotics and has increased sensitivity to erythromycin, chloramphenicol and doxycycline detergents and environmental noxae. This product can be administered 3 days after or before the administration of these chemotherapeutics which are effective against Salmonella. If this is inevitable, the flock must be re-immunized. Moreover, the efficacy of this product can be compromised by the simultaneous use of Gumboro, Eimeria and Marek live vaccines given at one day of age.

Field studies

One field study has been performed in two commercial farms during growing period and during laying period respectively. These farms were under strict control against *Salmonella* infections. It is expected that no infection be carried out on them. Consequently, a few animals were taken to other facilities in order to perform an experimental challenge at different stages of production to know the dissemination of the vaccine strain. According the obtained results, and regarding the safety assessment no adverse effects are produced in birds until the end of the laying period as a consequence of the vaccination.

Environmental 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 the potential exposure of the environment to the product is zero. No warnings regarding are therefore required.

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)

The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements which show that the vaccine reduces the persistence and the excretion of field strains through reducing internal organ colonization, by the results in the isolation of caecum, liver spleen, oviduct and ovaries samples from vaccinated birds, as well reducing the faecal excretion, by the results of the re-isolation from cloacal swabs from vaccinated birds. Moreover, it has been observed a reduction of Salmonella presence in environmental samples and eggs.

Efficacy of vaccination was demonstrated in 8 controlled laboratory challenge studies, by oral infection with a wild strain. At challenge 14-16 days after first vaccination, 20 days after the second vaccination and 1 month after third vaccination, the effects of the vaccine regarding colonization in internal organs and faecal excretion were confirmed in a higher percentage in unvaccinated control animals comparing to vaccinated animals.
The degree of relevant endpoint (colonization and shedding) was significantly decreased among vaccinated animals compared to control animals.
Summary table

Study	**Animals (Number/ groups)**	**Challenge (Day post- vaccination)**	**Parameters**	**Results**
Immunogenicity test	> 30 birds/group (3 groups)	D14	*Salmonella* detection in cloacae, liver, caecum and spleen	Lower level of colonisation in vaccinated comparing to controls
Immunogenicity test at laying and duration of immunity	≈ 20 birds/group (3 groups)	Week 81	*Salmonella* detection in cloacae, liver, caecum, spleen, ovary, and serum samples	Significant reduction in positive samples from vaccinated comparing to controls; difference in immune response. Egg production maintained.

Effects of MADs	> 15 birds/group (2 groups + 2 groups)	D16 D24	*Salmonella* detection in cloacae, liver, caecum and spleen	The study does not provide sufficient information that allows the proper evaluation of the efficiency of Nobilis SE live in the presence of MDAs. MDA -birds the vaccination reinforce the protection
Immunogenicity test and interactions	126 birds (5 groups)	D14 under an EU procedure prior to 1st January 2021 where the UK particip re, the contents of this Public Assessment Report are not owned by the e contact the original Reference Member State for any queries in relati	*Salmonella* detection in cloacae, liver, caecum, spleen and serum sam-	Interaction between vaccination and the use of Gumboro, Marek and Coccidiosis vaccines (inclusion in SPC).
			ples. Sera and biliary Samples.	
Reduction of faecal excretion	148 birds (2 groups)	D16	*Salmonella* detection in cloacae, liver, caecum and spleen	Significantly reduction of the shedding of the challenge strain in vaccinated comparing to controls.
Immunogenicity test after 2nd vaccination	>10 birds/groups (3 groups)	D28 post 2nd vaccination	*Salmonella* detection in cloacae, liver, caecum and spleen	Significantly differences in colonisation of the challenge strain between vaccinated and controls.
Immunogenicity test after 3rd vaccination	45 birds (3 groups)	D30 after the 3rd vaccination	*Salmonella* detection in cloacae, liver, caecum and spleen	Significantly differences in colonisation and reduction of excretion of the challenge strain between vaccinated and controls.

Field Trials

Animals	Challenge	Parameters	Efficacy asse ssment	Results
Growing pullet Farm: 16.620 birds vaccinated with PRIMUM and 21.552 birds vaccinated with Reference Product. Age: 20-22 weeks Laying farm: 15.147 birds vaccinated with PRIMUM and 19.628 birds vaccinated with	Two challenges: 4/5 weeks after 2nd vaccination and 30 days after the 3rd vaccination One challenge in the laying period	*Salmonella* detection in cloacae, liver, ovary, , caecum and spleen. Environmental samples. Egg samples.	Reduction of *Salmonella* after challenge in the field	After the first, second and third Challenge about shedding and colonization: The vaccine reduces th colonization (spleen, liver, ovar oviduct and caeca) and th shedding of the virulent strain. Significantly differences in colonisation and reduction of excretion of the challenge strain between vaccinated and control birds.

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Efficacy of vaccination was also demonstrated under field conditions in a controlled field trial including two farms with more than 30.000 birds each one. The vaccine was applied the first dose on 1 day of age, the second dose at week 8, and the third dose at week 19, by drinking water. Samples from different organs were taken, and also environmental samples and egg samples.

As a conclusion, the vaccine reduced the colonisation and the shedding of the virulent field strain.

Summary table

ce Product. Age: From 20-22 to 52 weeks				

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.

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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 (www.hma.eu).

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.

None