College ter Beoordeling van Geneesmiddelen / Medicines Evaluation Board

Graadt van Roggenweg 500
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The Netherlands

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Nobilis Salenvac ETC

NL/V/0305/001/DC

December 2022

MODULE 1

PRODUCT SUMMARY

EU Procedure number	NL/V/0305/001/DC
Name, strength and pharmaceutical form	Nobilis Salenvac ETC, suspension for injection
Applicant	Intervet International B.V. Wim de Körverstraat 35 5831AN Boxmeer The Netherlands
Active substance(s)	Inactivated *Salmonella* Enteritidis, strain PT4: 1 – 6.6 RP* Inactivated *Salmonella* Typhimurium, strain DT104: 1 – 16.1 RP Inactivated *Salmonella* Infantis, strain A, S03499-06: 1 – 26.6 RP *RP (relative potency): Ratio of antigenic mass (in Units) as compared to the antigenic mass (in Units) of a reference batch which was shown to be efficacious in chickens.
ATC Vetcode	QI01AB01
Target species	Chickens (breeders and layers)
Indication for use	For the active immunisation of chickens from 6 weeks of age to reduce colonisation and faecal excretion of *S.* Enteritidis (serogroup D), *S.* Typhimurium and *S.* Heidelberg (serogroup B), *S.* Infantis, *S.* Hadar and *S.* Virchow (serogroup C). <u>Onset of immunity after the second vaccination</u> − *S.* Enteritidis, *S.* Typhimurium, *S.* Infantis, *S.* Hadar and *S.* Virchow: 4 weeks − *S. Heidelberg*: 9 weeks* *Earliest timepoint investigated <u>Duration of immunity after the second vaccination</u> − *S.* Enteritidis: 48 weeks (evidenced by challenge) and 90 weeks (evidenced by serology) − *S.* Typhimurium: 57 weeks (evidenced by challenge) and 90 weeks (evidenced by serology) − *S.* Infantis: 51 weeks (evidenced by challenge) − *S.* Hadar: 51 weeks (evidenced by challenge) − *S.* Virchow: 51 weeks (drawn from scientific reasoning) − *S.* Heidelberg: 57 weeks (drawn from scientific reasoning)

MODULE 2

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Full application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	4 March 2020
Date product first authorised in the Reference Member State (MRP only)	N/A
Concerned Member States for original procedure	AT, BE, BG, CY, CZ, DE, EE, EL, ES, FR, HR, HU, IT, LT, LU, LV, 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 slight 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. Qualitative and quantitative particulars

The product contains the active substances inactivated *Salmonella* Enteritidis strain PT4 (1 - 6.6 RP), inactivated *Salmonella* Typhimurium strain DT104 (1 - 16.1 RP) and inactivated *Salmonella* Infantis strain A S03499-06 (1 - 26.6 RP), the adjuvant aluminium hydroxide, the preservative thiomersal and the excipients tris (trometamol), maleic acid, sodium chloride and water for injections.

The container/closure system consists of a low density polyethylene (LDPE) bottle, closed with a halogenobutyl stopper and sealed with an aluminium cap.

The choice of the vaccine strains and the choice of the composition is justified. The inactivation process and the detection limit of the control of inactivation are correctly validated. The product is a further development of Nobilis Salenvac and Nobilis Salenvac T, which have both been marketed for many years throughout Europe. 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 at a licensed manufacturing site.

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

C. Control of Starting Materials

The active substances are inactivated *Salmonella* Enteritidis, *Salmonella* Typhimurium and *Salmonella* Infantis. The active substances are manufactured in accordance with the principles of good manufacturing practice.

Biological starting materials used are in compliance with the relevant Ph. Eur. Monographs and guidelines.

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

Starting materials of non-biological origin used in production comply with pharmacopoeia monographs (Ph. Eur.) where these exist. For the substances where there is no such requirement the company has specified how quality is controlled.

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 potency, pH, aluminium content, formaldehyde content, thiomersal content, appearance, sterility, and fill volume.

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.

F. 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 when stored under the approved conditions.

The stability of the antigens when stored under the approved conditions has been demonstrated by formulating final product batches with aged antigens and performing real time stability of the finished product.

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

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Intervet International B.V.	DCP
	Publicly available assessment report

III. SAFETY ASSESSMENT

Nobilis Salenvac ETC is an inactivated vaccine containing aluminium hydroxide as an adjuvant. The antigen phase consists of inactivated *Salmonella* Enteritidis, *Salmonella* Typhimurium and *Salmonella* Infantis.

For this vaccine two specific monographs are applicable: 1947 “Salmonella Enteritidis Vaccine (Inactivated) For Chickens” and 2361 “Salmonella Typhimurium Vaccine (Inactivated) For Chickens”. For all laboratory and field safety studies performed with Nobilis Salenvac ETC, the setup according to Ph. Eur. monographs 1947, 2361 and 5.2.6. was followed.

Laboratory trials

The safety of the administration of one dose and the repeated administration of one dose in the target animal was performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines. The safety of a single dose and a repeated dose were investigated in three pivotal GLP studies, with three different vaccine batches, including 6-week old SPF chickens. Vaccination was performed at 6 weeks and 8 weeks of age of the study via intramuscular injection in the left breast. After the first vaccination, no clinicals signs, mortality or local reactions were observed. After the second vaccination, no clinical signs or mortality were observed, however transient local reactions, lasting 7-14 days and up to 8 mm in size were observed in some of the birds. It is concluded the vaccine is safe for single and repeated administration in chickens. The observed adverse events are described in section 4.6 of the SPC.

No investigation of effect on reproductive performance was conducted because the starting materials from which the product is derived are not considered a potential risk factor and the vaccine is not intended for use in birds in lay. An appropriate warning sentence is included in the SPC.

Since the antigens in this product are inactivated, it is not expected that this product might adversely affect the immune system of the vaccinated animal or its progeny. Therefore a specific study was not carried out.

The vaccine is inactivated and thus the specific tests to be performed for live vaccines are not applicable.

The adjuvant and excipients used are listed in Annex II of EC Regulation 2377/90. Based on this information, no withdrawal period is proposed.

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

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Field studies

Two safety and efficacy field studies were performed, one study in broiler breeders in the Netherlands and one study in pullets in the United Kingdom. The resulting safety data are presented in this section.

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results**	
Field study: field trial in the Netherlands					**Results**	**Conclusions**
Broiler breeders Group 1 (test group, vaccinated with ETC): 10,229 pullets Group 2 (positive control, vaccinated with T): 10,502 pullets	On day of vaccination: all chickens were seronegative for *S.* Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age Test vaccine: Nobilis Salenvac ETC Positive control vaccine: Nobilis Salenvac T Primary vaccination on day 0: IM into breast. Booster vaccination on day 48: IM into breast. Simultaneously, birds were vaccinated with other products.	-	General health: daily Feed intake: daily Local reactions (palpation): day 1, 4, 7 and 14 post (both) vaccination (PV) Egg production: daily until day 202 Mortality: daily until day 202	No systemic reactions observed during 14 days PV. No drop of feed intake observed 14 days PV Local reactions were not noted upon palpation. Mean daily egg production was 71.2% in the test group and 73.5% in the control group but both groups produced up to expectations.[b] The cumulative mortality (including culling) during the production period was 10.5% in the test birds and 11.0% in the controls.[b]	No adverse events were observed during the 14 day observation period after each vaccination and both test and control groups performed conform expectations. Egg production was within normal ranges in control and test groups. The data provided support the safety of the vaccine when applied under field conditions in broiler breeder pullets.

[b]: no significant difference between vaccinates and controls

Animals Groups Number Age	Antibody status	Vaccine: route of administration	Challenge: Day post-vaccination	Follow up: Duration Endpoints	Results	
Field study: field trial in the United Kingdom					**Results**	**Conclusions**
Layers Test Group 1 (vaccinated with ETC): 18,460 pullets Test Group 2 (vaccinated with ETC): 19,250 pullets Positive Control Group 1 (vaccinated with T): 18,460 pullets Positive Control Group 2 (vaccinated with T): 19,250 birds	On day of vaccination: all chickens were seronegative for *S.* Enteritidis, *S.* Typhimurium, *S.* Infantis	Test Group 1 and Positive Control Group 1: Vaccination at 7 and 15-16 weeks of age. Test Group 2 and Positive Control Group 2: Vaccination at 6 and 15-16 weeks of age. Test vaccine: Nobilis Salenvac ETC Positive control vaccine: Nobilis Salenvac T	-	General health: daily Feed intake: daily Local reactions (palpation): day 1, 4, 7, 14, 21 and 28 post (both) vaccination (PV) Egg production: daily until 38 weeks of age Mortality: daily until 38 weeks of age	Test group 2 and positive control group 2 were 'less active' on the first two days after first vaccination. Feed intake reduced in all 4 houses of one farm on the first day after the first vaccination. Local reactions were diffuse and <0.5 cm diameter after the first vaccination (but not after the second vaccination) in approximately 27-37% of test animals and 13-20% of controls. Mean daily egg production was 78% in the test group 1 and 77% in the control group 1, 82% in test group 2 and 83% in the control group 2.[b] Mortality was low and comparable between test and control groups.[b]	Mild transient systemic effects were observed in both test and control groups, but both groups performed conform expectations. The observed adverse events are included in the SPC. Egg production was within normal ranges in control and test groups. The data provided support the safety of the vaccine when applied under field conditions in layer pullets.

[b]: no significant difference between vaccinates and controls

User Safety

A risk assessment for user safety has been performed. Potential risk of skin exposure and self-administration are identified. Since excipients are considered safe and the vaccine strains are inactivated, the risks of accidental skin exposure or self-administration are considered to be low. The following sentence is included in the SPC to make the user aware of the potential risk:

"In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician."

Environmental Risk 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 risk of possible ecological effects of the inactivated antigens, the adjuvant, and of other substances present in the product is considered effectively zero.

Disposal of the unused vaccine should be done in accordance with local requirements, as mentioned in the SPC.

IV. CLINICAL ASSESSMENT (EFFICACY)

The ability of Nobilis Salenvac ETC to induce protection against *S*. Enteritidis, *S*. Typhimurium, *S*. Infantis infections were investigated in the efficacy studies. In addition, the ability of the vaccine to confer cross-protection against related serovars, namely *S*. Hadar, *S*. Heidelberg and *S*. Virchow was evaluated. Studies were designed in accordance with Ph.Eur. monographs 1947 and 2361.

Laboratory Trials

The applicant has conducted a total of twenty laboratory studies towards onset of immunity, duration of immunity and cross protection. The efficacy of the product has been demonstrated in laboratory studies in accordance with the relevant requirements, which show that vaccination of broiler breeders and layers with Nobilis Salenvac ETC from 6 weeks of age followed by a second vaccination after 4 weeks results in statistically significant reduction of shedding (faecal excretion) and internal organ colonization of *S.* Enteritidis, *S.* Typhimurium and *S*. Infantis in vaccinates as compared to controls. Cross-protection studies against *S*. Heidelberg, *S.* Hadar and *S*. Virchow confirmed that vaccination with Nobilis Salenvac ETC can confer protection against these serovars. Onset of immunity of 9 weeks (earliest timepoint investigated) for *S.* Heidelberg and 4 weeks for all other serovars was demonstrated. Duration of immunity as specified in the SPC was demonstrated for all serovars, except S. Virchow and S. Heidelberg.

Onset of immunity

A total of 7 onset of immunity/efficacy studies were performed, 3 for *S.* Enteritidis, 2 for *S.* Typhimurium and 2 for *S.* Infantis. The studies were performed with 6 week old SPF white leghorn layers, which were divided into two groups. One group was vaccinated at day 0 and 28 of the study, the other group consisted of unvaccinated controls. The birds were challenged when they were 14 weeks old, at day 56 of the study. After challenge, cloacal swabs were taken between at 1, and 14 and necropsy was performed at day 7, 10 and 14 after challenge to take samples of liver and spleen for culture. The onset of immunity against *S.* Enteritidis, *S*. Typhimurium and *S.* Infantis at 4 weeks after the second vaccination is supported by the data generated with minimum-potency and sub-potent vaccine batches in chickens of the youngest age recommended for vaccination. A significant reduction in shedding over the period of observation, both with respect to bacterial count and number of positive samples, as well as a significant reduction in colonisation of liver and (in particular) spleen with respect to bacterial load and number of positive samples was demonstrated.

Duration of immunity

One serology study was performed. Commercial laying hens were allocated to two groups. In the treatment group, chickens were vaccinated at 6 and 10 weeks of age, the control group remained unvaccinated. To determine the serological responses elicited by Nobilis Salenvac ETC, antibody levels against flagella antigens from *S*. Enteritidis, *S*. Typhimurium and *S*. Infantis were tested by ELISA following vaccination, until 100 weeks of age in vaccinated and unvaccinated birds. Antibody levels against *S.* Enteritidis and *S.* Typhimurium were relatively stable over the tested period. Duration of immunity of 90 weeks is demonstrated by serology for *S.* Enteritidis and *S.* Typhimurium.

A total of 6 duration of immunity studies were performed, 3 for *S.* Enteritidis, 2 for *S.* Typhimurium and 1 for *S.* Infantis. The studies were performed with 6 week old female hyline brown commercial layers, which were divided into two groups. One group was vaccinated at day 0 and 28 of the study, the other group consisted of unvaccinated controls. The birds were challenged ranging from 46 – 72 weeks post vaccination. After challenge, cloacal swabs were taken between day 1 and 14 and necropsy was performed at day 7, 10 and 14 after challenge to take samples of liver and spleen for culture. For *S.* Enteritidis, a significant reduction in shedding was shown after challenge at 48 weeks post vaccination and a significant reduction in organ colonisation was shown after challenge at 57 weeks post vaccination, based on which a duration of immunity of 48 week is considered demonstrated. For *S.* Typhimurium a numerical reduction in the number of *Salmonella* isolated from cloacal swabs was found after challenge at 57 weeks post vaccination, based on which a duration of immunity of 57 weeks is considered demonstrated. For *S.* Infantis, a reduction of shedding and colonisation is demonstrated after challenge at 51 weeks post vaccination.

Cross protection

The vaccine strain *S*. Typhimurium included in Nobilis Salenvac ETC shares common somatic antigens with *S*. Heidelberg and the vaccine strain *S*. Infantis shares common somatic antigens with *S*. Hadar and *S*. Virchow. Challenge studies were performed to investigate cross protection. A total of 5 cross protection studies were performed, 3 for *S.* Hadar, 1 for *S.* Heidelberg and 1 for *S.* Virchow. The studies were performed in 6 week old mixed sex white leghorn SPF birds, which were divided into two groups. One group was vaccinated at day 0 and 28 of the study, the other group consisted of unvaccinated controls. Challenge with *S.* Hadar was performed at 4, 51 and 72 weeks post challenge. Challenge with *S.* Heidelberg was performed at 9 weeks post vaccination and challenge with *S.* Virchow at 4 weeks post vaccination. Cloacal swabs were taken between day 1, and 14 and necropsy was performed at day 7, 10 and 14 after challenge to take samples of liver and spleen for culture. From the data provided, the claim for cross-protection against *S.* Hadar, *S.* Virchow and *S.* Heidelberg, by a reduction in shedding and colonization, was shown at 4 weeks (*S.* Hadar, *S.* Virchow), 9 weeks (*S.* Heidelberg) and 51 weeks (*S.* Hadar). A duration of immunity of 51 weeks for *S.* Vichow and 57 weeks for *S.* Heidelberg was determined by scientific reasoning (based on duration of immunity up to 51 weeks for *S*. Infantis and duration of immunity up to 57 weeks for *S.* Typhimurium, respectively).

Effects of maternally derived antibodies

Efficacy data generated using Nobilis Salenvac T are used in support of the *S.* Enteritidis and *S.* Typhimurium components of Nobilis Salenvac ETC, since the components of these vaccines are identical with the exception of the number of active substances. Passive immunity studies performed with Nobilis Salenvac T demonstrated that maternally derived antibodies (MDA) are transferred from 4 weeks after the second vaccination up to 59 weeks of age of the parent bird and the duration of immunity is until 14 days after hatching. Based on this, it can be concluded that at 6 weeks of age, MDA would have declined.

Field Trials

Two safety and efficacy field studies were performed, one study in broiler breeders in the Netherlands and one study in pullets in the United Kingdom. The resulting efficacy data are presented in this section.

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results**	
Field study: field trial in the Netherlands [combined safety and efficacy trial]					**Results**	**Conclusions**

Broiler breeders Group 1 (test group, vaccinated with ETC): 10,229 pullets Group 2 (positive control, vaccinated with T): 10,502 pullets	On day of vaccination: all chickens were seronegative for *S.* Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age Test vaccine: Nobilis Salenvac ETC Positive control vaccine: Nobilis Salenvac T Primary vaccination on day 0: IM into breast. Booster vaccination on day 48: IM into breast. Simultaneously, birds were vaccinated with other products.	-	Infection with *Salmonella* Antibody response Lab trials	Study birds remained *Salmonella* negative throughout the study. For *S.* Enteritidis and *S.* Typhimurium. The serological response of both vaccination groups was comparable. Highest titres were observed 6 weeks after second vaccination and remained at a high level up to the last sampling (week 46 of the study). A similar pattern was observed for *S.* Infantis in the test group 1, while controls remained seronegative throughout the study. Efficacy was evaluated by laboratory challenges on chickens taken from this field study, see below for summary of these studies.	It can be concluded that Salenvac T and Salenvac ETC induce a similar antibody response for *S.* Enteritidis and *S.* Typhimurium. The immune response for the *S.* Infantis component in Salenvac ETC was of similar magnitude.
Field efficacy/lab challenge: Broiler breeders challenged with *Salmonella* Enteritidis					**Results**	**Conclusions**
Broiler breeders Group 1 (test group, vaccinated with ETC): 60 pullets Group 2 (control group, unvaccinated): 60 pullets	On day of vaccination: all chickens were seronegative for *S.* Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age IM into breast Test vaccine (group 1): Nobilis Salenvac ETC Control (group 2) was not vaccinated against *Salmonella*.	Challenged with *S.* Enteritidis at 163 days of age (6 weeks post vaccination)	Cloacal swabs at day 3, 5, 7, 11 and 14 PC Necropsy at day 6 and 10 PC.	Total shedding over time (day 3-14) and number of birds shedding was lower in the vaccinates compared to controls.[a] Combined direct bacterial count in liver and spleen was reduced in the vaccinates.[a] The number of total positive samples was lower in the vaccinates.[a]	Statistically significant reduction of *Salmonella* shedding and colonisation after vaccination with Nobilis Salenvac ETC.

Field efficacy/lab challenge: Broiler breeders challenged with *Salmonella* Typhimurium					**Results**	**Conclusions**
Broiler breeders Group 1 (test group, vaccinated with ETC): 60 pullets Group 2 (control group, unvaccinated): 60 pullets	On day of vaccination: all chickens were seronegative for *S*. Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age IM into breast Test vaccine (group 1): Nobilis Salenvac ETC Control (group 2) was not vaccinated against *Salmonella*.	Challenged with *S.* Typhimurium at 163 days of age (6 weeks post vaccination)	Cloacal swabs at day 3, 5, 7, 11 and 14 PC Necropsy at day 6 and 10 PC.	Total shedding over time (day 3-14) and number of birds shedding was lower in the vaccinates compared to controls.[a] Combined direct bacterial count in liver and spleen was reduced in the vaccinates.[a] The number of total positive samples was only numerically lower in the vaccinates.[b]	Statistically significant reduction of *Salmonella* shedding (load and percentage of positives) and colonisation (load, but not number of positives) after vaccination with Nobilis Salenvac ETC.
Field efficacy/lab challenge: Broiler breeders challenged with *Salmonella* Infantis					**Results**	**Conclusions**
Broiler breeders Group 1 (test group, vaccinated with ETC): 60 pullets Group 2 (control group, unvaccinated): 60 pullets	On day of vaccination: all chickens were seronegative for *S*. Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age IM into breast Test vaccine (group 1): Nobilis Salenvac ETC Control (group 2) was not vaccinated against *Salmonella*.	Challenged with *S.* Infantis at 184 days of age (9 weeks post vaccination)	Cloacal swabs at day 3, 5, 7, 11 and 14 PC Necropsy at day 6 and 10 PC.	Total shedding over time (day 3-14) and number of birds shedding was lower in the vaccinates compared to controls.[a] Combined direct bacterial count in liver and spleen was reduced in the vaccinates.[a] The number of total positive samples was lower in the vaccinates.[a]	Statistically significant reduction of *Salmonella* shedding and colonisation after vaccination with Nobilis Salenvac ETC.
Field efficacy/lab challenge: Broiler breeders challenged with *Salmonella* Hadar [cross protection]					**Results**	**Conclusions**
Broiler breeders Group 1 (test group, vaccinated with ETC): 60 pullets Group 2 (control group, unvaccinated): 60 pullets	On day of vaccination: all chickens were seronegative for *S*. Enteritidis, *S.* Typhimurium, *S.* Infantis	Vaccination at 10 and 17 weeks of age IM into breast Test vaccine (group 1): Nobilis Salenvac ETC Control (group 2) was not vaccinated against *Salmonella*.	Challenged with *S.* Hadar at 184 days of age (9 weeks post vaccination)	Cloacal swabs at day 3, 5, 7, 11 and 14 PC Necropsy at day 6 and 10 PC.	Total shedding over time (day 3-14) and number of birds shedding was lower in the vaccinates compared to controls.[a] Combined direct bacterial count in liver and spleen and the total positive samples was only numerically reduced in the vaccinates.[b]	Statistically significant reduction of *Salmonella* shedding after vaccination with Nobilis Salenvac ETC. However, reduction of organ colonisation was not shown.

[a]: significant difference between vaccinates and controls
[b]: no significant difference between vaccinates and controls

Animals Groups Number Age	**Antibody status**	**Vaccine: route of administration**	**Challenge: Day post-vaccination**	**Follow up: Duration Endpoints**	**Results**	
Field study: field trial in the United Kingdom [combined safety and efficacy trial]					**Results**	**Conclusions**
Layers Test Group 1 (vaccinated with ETC): 18,460 pullets Test Group 2 (vaccinated with ETC): 19,250 pullets Positive Control Group 1 (vaccinated with T): 18,460 pullets Positive Control Group 2 (vaccinated with T): 19,250 birds	On day of vaccination: all chickens were seronegative for *S*. Enteritidis, *S.* Typhimurium, *S.* Infantis	Test Group 1 and Positive Control Group 1: Vaccination at 7 and 15-16 weeks of age. Test Group 2 and Positive Control Group 2: Vaccination at 6 and 15-16 weeks of age. Test vaccine: Nobilis Salenvac ETC Positive control vaccine: Nobilis Salenvac T	-	Infection with *Salmonella* Antibody response	Birds were seronegative for all three antigens on the day of vaccination. Antibody responses to *S.* Enteritidis reached a maximum at 5 weeks after the second vaccination and remained at a similar level up to 41 weeks p.v.. Antibodies to *S.* Typhimurium reached highest level at 5 weeks p.v. in the controls and at 23 weeks p.v. in the test group. Levels slightly decreased in week 41 p.v.. For *S.* Infantis, a very small response was observed in the controls whereas a clear response was seen in the test group. A maximum was observed at 5 weeks p.v. while titres slightly decreased thereafter.	The data show that vaccination with Nobilis Salenvac ETC induces production of antibodies against all the antigens included in the vaccine and this serological response persisted until 41 weeks after vaccination. Furthermore, the level of serological responses generated were similar to those obtained with the licensed vaccine “Nobilis Salenvac T”.

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 Heads of Veterinary Medicines 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.

Summary of change	**Section updated**	**Approval date**
Change in the name of the MAH in the UK (IE/V/xxxx/IA/166/G)	N/A	15 July 2020
Change in the name of the active substance manufacturer (IE/V/xxxx/IA/167/G)	N/A	14 August 2020
Change in the name of a manufacturer responsible for batch release (IE/V/xxxx/IA/168/G)	N/A	05 September 2020
Addition of final product QC testing site in the EU (NL/V/0305/II/004/G)	N/A	09 December 2021
Extension of the shelf-life of the antigens and the finished product and update of the product I formation to QRD v9.0 (NL/V/0305/A/005/G)	N/A	07 December 2022