MINISTERIO DE SANIDAD
agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS VETERINARIOS

Agencia Española de Medicamentos y Productos Sanitarios

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28022 – Madrid
España
(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

PRIMUN SALMONELLA T Lyophilisate for use in drinking water for chicken

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MODULE 1

PRODUCT SUMMARY

EU Procedure number	ES/V/0408/001/DC
Name, strength and pharmaceutical form	PRIMUN SALMONELLA T Lyophilisate for use in drinking water for chickens
Applicant	Laboratorios Calier S.A. Calle Barcelones 26 Pla De Ramassar Les Franqueses Del Vallès Barcelona
Active substance(s)	Live, attenuated *Salmonella enterica* subsp. *enterica* serovar Thyphimurium-strain ST CAL 16 Str+/Rif+/Enr-
ATC Vetcode	QI01AE01
Target species	Chickens (Replacement chicks: future layers and breeders)
Indication for use	Active immunisation of chickens (future layers and breeders) to reduce faecal excretion and colonisation of internal organs with Salmonella Typhimurium field strains.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on in the Union Product Database (UPD).

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	30/03/2022
Date product first authorised in the ReferenceMemberState (MRP only)	-
Concerned Member States for original procedure	DE, IT, PL, PT

I. SCIENTIFIC OVERVIEW

The vaccine is a live bacteria which is indicated for the immunisation of chickens (future layers and breeders) to reduce faecal excretion and colonisation of internal organs with Salmonella Typhimurium field strains. The active substance is *Salmonella enterica subsp. enterica serovar Typhimurium*, strain CAL 16 Str+/Rif+/Enr-.

The recommended vaccination scheme is as follows: One dose from one day of age (in the first 72 hours), followed by a second vaccination at 6 to 8 weeks of age and a third vaccination at 14-18 weeks, but at least 4 weeks before the onset of the laying period.

The IVMP is manufactured and controlled using validated methods and tests that ensure the consistency of the IVMP released on the market.

The IVMP can be safely used in the target species;

The IVMP is also 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 IVMP was demonstrated according to the claims made in the SPC.

The overall risk/benefit analysis is in favour of granting a marketing authorisation for this IVMP.

II. QUALITY ASPECTS

A. Qualitative and quantitative particulars

The IVMP contains *Salmonella enteric subsp. enterica serovar Typhimurium,* strain CAL 16 Str+/Rif+/Enr-. The excipients included are saccharose (stabilizer), gelatine (cryoprotective), skimmed milk, HEPES buffer and water for injections, which is in line with the rest of the vaccines actually present in the market of the same characteristics.

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

The lyophilisate is filled in glass type I containers, closed with bromobutyl rubber stoppers and sealed with aluminium caps in 1.000 and 2.000 doses presentations. It can be also marketed in cardboard boxes with 10 vials.

The choice of the vaccine strain is justified.

The selection of the manufacturing process of the active substance and the finished product is explained.

B. Method of Preparation of the Product

The IVMP is manufactured fully in accordance with the principles of good manufacturing practice at a licensed manufacturing site.

Process validation data on the IVMP are provided in accordance with the relevant European guidelines.

C. Control of Starting Materials

Starting materials of non-biological origin used in production comply with European pharmacopoeia monographs where these exist, 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 ""Guideline on requirements for the production and control of immunological veterinary medicinal products" (EMA/CVMP/IWP/206555/2010-Rev01).

The master and working seeds were produced according to the seed lot system as described in the relevant guideline.

Scientific data and/or 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.

D. Control tests during production

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

In-process control tests are carried out on intermediate stages of manufacture in order to verify the consistency of the manufacturing process and the final IVMP.

A specification was set for each intermediate and the analytical methods are described and validated, if applicable.

A shelf life and storage conditions for the intermediate IVMP are defined based on data resulting from stability studies.

E. Control Tests on the Finished Product

For all tests, a short description of the techniques for analysing the finished product is provided. The tests and their specifications and limits are justified and are considered appropriate to adequately control the quality of the IVMP.

Satisfactory validation data for each analytical methods are provided, if appropriate.

The tests performed on the final product conform to the relevant requirements and monographs, if applicable; any deviation from these requirements is justified.

Batch analytical data from the proposed production sites are provided demonstrating compliance with the determined specification.

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

F. Batch-to-batch consistency

Full protocols of three consecutive batches of the product, representative of the routine production and giving the results for all tests performed during production and on the finished product, are provided in order to ensure that quality is consistent from batch to batch and to demonstrate conformity with the predefined specifications.

G. Stability

Stability data on the finished product are provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life (2 years) when stored under the approved conditions (at 2-8° C).
The vaccine must be used within 3 hours after reconstitution.

H. Other Information

III. SAFETY ASSESSMENT

The safety of the IVMP when administered to the target species, the potential harmful effects (residues in IVMP, substance in foodstuff), the potential serious risk for human beings during product administration and to the environment are adequately described.

Laboratory trials

The safety of the administration of an overdose (only for live IVMP) and the repeated administration of one dose to the target animal was demonstrated in SPF day-old chicks. Twenty-four chicks were vaccinated with a vaccine overdose (10X) at one day of age and two weeks later with one dose of the vaccine by the oral route. In order to assess the safety of the vaccine several parameters were monitored (general clinical signs, mortality rates, body weights, litter samples and cloacal swabs)

No investigation of effects on the reproductive performance was conducted the IVMP cannot compromise the reproductive function due to the incapacity of the strain to replicate in the reproductive organs. The colonisation of these organs (ovary and oviduct) and the possibility of egg contamination was evaluated in the dissemination studies.

There are no data suggesting that this product might adversely affect the immune system of the vaccinated animal or its progeny. Therefore, no specific study was carried out.

For the bacterial strain included in the vaccine specific studies were carried out to describe the spread, dissemination, reversion to virulence, biological properties, recombination or genetic reassortment of the vaccine strain.

Salmonella sp. is included in the list of biological substances not requiring MRL evaluation according to Commission Regulation (EU) 2018/782.

The adjuvant and excipients used are saccharose (stabilizer), gelatine (cryoprotective), skimmed milk, HEPES buffer and water for injections, which is in line with the rest of the vaccines actually present in the market of the same characteristics.

A withdrawal period of 28 days for meat and offals after the first and second vaccination and 14 days after the third vaccination is justified, as it is a live vaccine for a zoonotic disease.

The assessment of the interaction of this product with Primun Salmonella E vaccine was made. The safety and efficacy of this association of vaccines when mixed are demonstrated. Suitable warnings are included in the SPC and package leaflet.

Details are given in the Summary of Product Characteristics (SPC) as follows:

3.6 Adverse events

None known.

3.7 Use during pregnancy, lactation or lay

Laying birds

The safety of the veterinary medicinal product has not been established during lay.

Do not use in birds in lay and within 4 weeks before the start of the laying period.

3.8 Interaction with other medicinal products and other forms of interaction

Since the vaccine strain consists of live bacteria, simultaneous use of chemotherapeutics, which are effective against Salmonella should be avoided. However, if this is inevitable, the flock must be re-immunised. A decision to use this vaccine before or after any chemotherapeutic treatment needs to be taken on a case-by-case basis.

No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product, so 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.

Studies presented with a combined formulation of PRIMUN Salmonella E+T vaccine indicates that no negative interactions have been shown.

3.10 Symptoms of overdose (and where applicable, emergency procedures, antidotes)

No adverse reactions were detected after a 10-fold overdose.

Field studies

Two safety studies were designed for the evaluation of the safety and efficacy of the vaccine under field conditions.
The results confirm the observations made in the laboratory studies. The local and systemic reactions observed are described in the SPC and package leaflet under “adverse reactions”.

Ecotoxicity
The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline, which showed that no further assessment is required.

Warnings and precautions as listed in the product literature are adequate to ensure safety to the environment when the product is used as directed.

Details are given in the Summary of Product Characteristics (SPC) as follows:

3.5 Special precautions for use

Special precautions for safe use in the target species

Vaccinated chickens may excrete the vaccine strain up to 28 days following vaccination. During this time, the contact of immunosuppressed and unvaccinated chickens with vaccinated chickens should be avoided.
Appropriate veterinary and husbandry measures should be taken to avoid spread of the vaccine strain to susceptible species. An effective rodent control program should be established, as infected mice may also spread the vaccine strain.

Special precautions to be taken by the person administering the veterinary medicinal product to animals

The vaccine strain can be found in the environment for up to 28 days.

IV. CLINICAL ASSESSMENT (EFFICACY)

To demonstrate the efficacy of the IVMP several parameters were assessed according to the specific Ph. Eur. monograph 2521.

Laboratory trials
The efficacy of the product was demonstrated in laboratory studies under well-controlled conditions in accordance with the relevant requirements, which show that the onset of immunity is established 14 days after first vaccination and the duration of immunity lasts 61 weeks after the third vaccination, when used according to the recommended vaccination schedule.

The proposed vaccination schedule is: A single dose from one day of age (in the first 72 hours), followed by a second vaccination at 6 to 8 weeks of age and a third vaccination at 14-18 weeks at least 4 weeks before the onset of the laying period.

To demonstrate the efficacy of the vaccine, six different laboratory studies and two field trials have been carried out in compliance with the relevant requirements and guidelines.

Pre-clinical efficacy studies conducted are as follows:

• Strain selection was demonstrated in two laboratory studies:

- "Colonization and faecal excretion of different clones of Salmonella Typhimurium and degree of protection against field strain infections". To evaluate the colonization, faecal excretion and ability of 2 vaccine candidates at 2 different titre to protect chickens of the minimum age to be recommended for vaccination from field strain infection, according to requirements of Ph. Eur. 2521 *Salmonella* Typhimurium vaccine (Live, Oral) for Chickens point 2,2,2,1, Immunogenicity.

- "Degree of protection against field strain infection of a combined vaccine of Salmonella Enteritidis and *Salmonella* Typhimurium in poultry" To evaluate the ability of two combined vaccines to protect chickens at 1 day of life from field strain infections of the same serovars and to compare the protection with a reference vaccine. The study design also includes different Salmonella T strains to the vaccine strain.

• The selection of minimum dose was demonstrated in one laboratory study:

-"Degree of protection against field strain infections of different combinations of Salmonella Enteritidis and Salmonella Typhimurium vaccines in poultry" This assay was designed to study the reduction in colonization and excretion in one day old SPF chickens that were vaccinated with 3 different combinations of the strain Sm+/Rif+/Ssq- of Salmonella Enteritidis and the strain SmR/RifR/EnrS of Salmonella Typhimurium and a reference vaccine.

• The Immunogenicity of the vaccine and OoI was demonstrated in two laboratory studies:

-"Study of the dissemination, excretion and protection degree of vaccine strain of Salmonella Typhimurium after challenge with a field strain". 65 SPF eggs were used for the study and distributed in two groups. 32 animals were vaccinated with one dose by orogastric gavage at 1 day of age and 33 control animals remained without vaccination. All the animals involved in the study were challenged. For examination of the vaccine

bacteria the applicant describes the methodology employed for the cloacal swabs and internal organs.

- "Immunogenicity test of *Salmonella* Typhimurium vaccine after first vaccination by oral and spray route in SPF birds". This study was intended to compare the efficacy of the vaccine after first spray vaccination with the efficacy of a first oral vaccination in 1 day old SPF birds. Chickens were challenged at 14 days after first vaccination. The objective of the study was to demonstrate that the vaccinated chickens (vaccinated via oral and spray) in laboratory conditions reduce excretion and/or colonisation of challenge bacteria compared to a control group.

• The Immunogenicity of the vaccine at the end of laying period and DoI was demonstrated in one laboratory study and in two field studies.

- "Immunogenicity test of combined *Salmonella* Enteritidis and *Salmonella* Typhimurium at the end of the laying period". Laboratory study intended to determine the efficacy of the vaccine after the full vaccine schedule recommended and comparing the excretion and colonization of the challenge strain in vaccinated animals with the excretion and colonization of control animals. Animals were vaccinated by orogastric gavage.

Field studies
The Immunogenicity of the vaccine at the end of laying period and DoI was demonstrated in one laboratory study and in two field studies.

- "Evaluation of the safety and efficacy of Primun Salmonella T vaccine in pullets under field and experimental conditions". This report includes results of safety of the vaccine in pullets after three vaccinations and until the end of laying. In addition, comprises the results of efficacy (immunogenicity test) of the vaccine until the end of laying period.

- "Evaluation of the safety and efficacy of Primun Salmonella T vaccine against *S.Typhimurium* in pullets under field conditions".
A total of 135.700 pullets sourced from a commercial hatchery were enrolled in the study and distributed in 4 groups. Two groups, one with 33.700 and other with 43.000 pullets were vaccinated with Primun Salmonella T and a third group of 59.000 pullets were vaccinated with an authorized vaccine. 100 animals were maintained as controls.

The animals were vaccinated at week 1, at week 7 and at week 14 of age orally or by spray administration. The administration of the product by drinking water was given on day 3 (group 1 with Primun Salmonella T) or by the spray route was given at day 1 (group 2 with Primun Salmonella T) and in all cases the vaccination was given by drinking water at week 7 and at week 14. Dose used was 2.71 $x10^8$ CFU/animal.

The objective of the study is to demonstrate that PRIMUN SALMONELLA T protect hens until 75 weeks of age, so the duration of immunity can be established until 61 weeks after vaccination with 3rd dose.

The following conclusions can be drawn from the results of the studies concerning onset and duration of immunity, indications for use and immunisation scheme:

3.2 Indications for use for each target species

Active immunisation of chickens (future layers and breeders) to reduce faecal excretion and colonisation of internal organs with Salmonella Typhimurium field strains.
Onset of immunity: 14 days after first vaccination.
Duration of immunity: 61 weeks after the third vaccination, when used according to the recommended vaccination schedule.

3.8 Interaction with other medicinal products and other forms of interaction

Since the vaccine strain consists of live bacteria, simultaneous use of chemotherapeutics, which are effective against Salmonella should be avoided. However, if this is inevitable, the flock must be re-immunised. A decision to use this vaccine before or after any chemotherapeutic treatment needs to be taken on a case-by-case basis.
No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product, so 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.
Studies presented with a combined formulation of PRIMUN Salmonella E+T vaccine indicates that no negative interactions have been shown.

3.9 Administration routes and dosage

For oral use after resuspension in drinking water.
Recommended vaccination scheme:
One dose from one day of age (in the first 72 hours), followed by a second vaccination at 6 to 8 weeks of age and a third vaccination at 14-18 weeks, but at least 4 weeks before the onset of the laying period.
Advice on correct administration via drinking water:
Make sure that all conduit pipes, tubing, troughs, drinkers etc. are thoroughly clean and free of any traces of disinfectants, detergents, soap etc. Use only cold, clean and fresh drinking water, free of chlorine and metal ions.
Open the vaccine bottle under water and dissolve thoroughly in a 1-litre vessel half-full and stir well before mixing the solution with more water. As the concentrated vaccine is slightly viscous, care should be taken to empty the bottle and its top completely by rinsing them in water. Then add water until there is a volume of 1 litre in the same vessel. The vaccine must be stirred thoroughly for several minutes at each stage. Do not split large bottles for use in more than 1 poultry house or drinking system, as this leads to dosing errors.
As a guide apply the reconstituted vaccine to cold and fresh water at a rate of 1 litre of drinking water per 1,000 1-day-old chicks, 25-35 litres of water per 1,000 6-8 week-old birds and 35-40 litres of water per 1,000 14-18 week-old birds.. Use water meter recordings for the previous day to determine accurately the correct quantity of water in each case. Low fat skimmed milk powder (i.e. <1 % fat) is recommended to be added to the water (2-4 grams per litre) or skimmed milk (20-40 ml per litre of water) to increase the stability of the vaccine.
Allow water in the drinkers to be consumed so that levels prior to vaccine application are minimal. If water is still present, the lines must be drained before applying the vaccine. The ready-to-use vaccine solution should be consumed within 3 hours. It should be ensured that all birds drink during this period. Birds drinking behaviour varies. Therefore, it may be necessary to withhold drinking water on some sites prior to vaccination in order to ensure that all birds drink during the vaccination period. The aim is to apply to every

bird one dose of vaccine. A period of thirst of up to 2-3 hours depending on the actual climatic conditions before vaccination may be necessary to achieve this.

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 are 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 in the Union Product Database (UPD).

This section contains information on significant changes agreed after the original procedure, which are important for the quality, safety or efficacy of the product.