ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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(Reference Member State)

DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

GALLIMUNE Se + St, water-in oil emulsion for injection

PuAR correct as of 07/06/2018 when RMS was transferred to DE.
Please contact the RMS for future updates

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0001/001/DC
Name, strength and pharmaceutical form	Gallimune Se + St, water-in oil emulsion for injection
Applicant	Merial Animal Health Ltd PO Box 327 Sandringham House Harlow Business Park Harlow Essex CM19 5TG
Active substances	Inactivated *Salmonella* Enteritidis PT4 Inactivated *Salmonella* Typhimurium DT104
ATC Vetcode	QI01AB01
Target species	Chickens (layer pullets)
Indication for use	For active immunisation of layer pullets to: reduce *Salmonella* Enteritidis dissemination in the ovary, as demonstrated 4 days after challenge; This has been tested 25 weeks after vaccination and has been demonstrated to persist until 58 weeks of age. - reduce *Salmonella* Typhimurium and *Salmonella* Enteritidis dissemination in the intestinal tract. This has been tested 4 weeks after vaccination and has been demonstrated to persist until 61 weeks of age for *Salmonella* Typhimurium and 52 weeks of age for *Salmonella* Enteritidis.

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	Decentralised application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	11th June 2007
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria Belgium Cyprus Czech Republic Denmark France Germany Greece Hungary Ireland Italy Latvia Lithuania Luxembourg The Netherlands Poland Portugal Slovakia Slovenia Spain

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. Composition

The product contains Inactivated *Salmonella* Enteritidis PT4 and Inactivated *Salmonella* Typhimurium DT104 and excipients paraffin oil, thiomersal, formaldehyde, esters of fatty acids and ethoxylated polyols, ester of fatty acids and polyols and water for injections.

The product is supplied in 300 ml polypropylene bottles with a nitrile elastomer closure with an aluminium cap. Each bottle contains 1000 doses of vaccine and may be supplied in packs of 10 bottles. The particulars of the containers and controls performed are provided and conform to the regulation. The choice of the adjuvant, preservative and vaccine strain are justified. The inactivation process and the detection limit of the control of inactivation are correctly validated.

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 and relevant European guidelines.

C. Control of Starting Materials

The active substances are Inactivated *Salmonella* Enteritidis PT4 and Inactivated *Salmonella* Typhimurium, established active substances. An adequate summary of the origin of the two strains of *Salmonella* used has been provided.

Starting materials of non-biological origin used in production comply with relevant European pharmacopoeia monographs.

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 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 appearance, volume, assay of the active ingredients, density, viscosity, thiomersal concentration, formaldehyde concentration, sterility, inactivation and safety.

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. Other supportive data provided confirm the consistency of the production process.

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

H. Genetically Modified Organisms

Not applicable.

J. Other Information

Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 18 months.
Shelf-life after first opening the immediate packaging: use immediately after opening.

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

- This product contains mineral oil. Accidental injection/self injection may result in severe pain and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given.
- If you are accidentally injected with this product, seek prompt medical advice even if only a very small amount is injected and take the package leaflet with you.
- If pain persists for more than 12 hours after medical examination, seek medical advice again.

To the physician:

- This product contains mineral oil. Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even the loss of a digit. Expert, PROMPT, surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon.

III. SAFETY ASSESSMENT

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 laboratory studies. The investigations were performed according to the recommendations of Directive 2001/82/EC as amended and the relevant guidelines.

Birds were of minimum age and the schedule was as according to recommendations. At the age at which most layers are slaughtered (and may enter the food chain indirectly) all birds had some residual oily deposits and some had fibrosis and granulomas. Findings are accurately reflected in the SPC:

No palpable reactions were observed following the injection of one dose of vaccine. Small lesions linked to the oily adjuvant, e.g. small quantities of oily residues, were observed at the injection site three weeks after the injection and may persist through lay and decline over time.

Effects on reproductive performance were examined in two studies. One study examined reproductive safety in minimum age birds using a high antigen input batch and the intramuscular route of administration. Safety to 31 weeks of age was examined and it was concluded that this was sufficient to demonstrate safety across lay. The second study gives supportive evidence to the reproduction safety of the vaccine when administered by the intramuscular route. A standard batch was used and the birds were above minimum age.

These results are reflected in the SPC:

A slight delay in the onset of lay may be observed, however no impact on peak production or overall egg productivity has been observed.

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.

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 Council Regulation 2377/90 and therefore can be included in products used in food producing animals without a maximum residue limit. Based on this information, the withdrawal period has been set at zero days.

The absence of interaction of the vaccine with Gallimune 407 (vaccine for chickens against Egg Drop Syndrome (EDS76), Newcastle Disease, Infectious Bronchitis and Avian Rhiniotracheitis was demonstrated. Information relating to this is provided on the SPC:

No information is available on the safety and efficacy from the concurrent use of this vaccine with any other except inactivated vaccines for chickens of Merial Gallimune range against Egg Drop Syndrome (EDS76), Newcastle Disease, Infectious Bronchitis (Mass41) and Avian Rhinotracheitis (Swollen Head Syndrome). It is therefore recommended that no other vaccines should be administered within 14 days before or after vaccination with the product.

Field studies

Data from one large field study where birds were vaccinated by the intramuscular route has been provided which substantiated the findings of the laboratory studies in terms of weight effects and egg production. Information relating to this is provided on the SPC:

A slight delay in the onset of lay may be observed, however no impact on peak production or overall egg productivity has been observed.

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 on the product literature are adequate to ensure safety to the environment when the product is used as directed.

Any unused product or waste material should be disposed of in accordance with local requirements.

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. Bibliographical data in support of the efficacy of the product has also been provided in some cases.

Three studies have been provided which show that there is serological conversion[1] after vaccination with Gallimune Se + St in conventional hens using the recommended vaccination schedule by the intramuscular route. Published literature has also been provided in support of the predominant protective antigen.

A challenge study giving information regarding the onset of immunity was provided. This provides evidence of a reduction in isolation of the challenge strain when birds below minimum age were vaccinated once at 3 weeks of age with a reduced formulation administered by the intramuscular route and challenged 4 weeks post vaccination.

Another challenge study investigated the protection against *Salmonella* Enteritidis in 31 week old laying hens. Layers were vaccinated twice by the intramuscular route using a batch of target formulation. There was a reduction in shedding of the strain in the vaccinated groups. This was statistically significant. The study demonstrated that vaccination reduces excretion and gives some evidence regarding duration of immunity.

A similar challenge study was conducted involving *Salmonella* Typhimurium. One group of layers were vaccinated twice by the intramuscular route using a batch of target formulation and another group were vaccinated in the same way using a reduced formula. The study demonstrated that vaccination with a reduced formulation reduces excretion and gives some evidence regarding duration of immunity.

Two studies were provided relating to the duration of immunity against *Salmonella* Enteritidis. In one of the studies at 4 days post challenge (challenge occurred at 58 weeks of age) hens were euthanased and ovaries were removed from all birds and analysed for *Salmonella* Enteritidis. The study showed that vaccination with either a target or reduced formula batch leads to a reduction in *Salmonella* Enteritidis isolation from the ovaries, demonstrating that the vaccine protects across lay. In the second study individual faecal samples were collected (challenge occurred at 52 weeks of age). Results indicated that vaccination with the reduced formulation induced a reduction in *Salmonella* Enteritidis excretion after challenge in laying hens at the end of lay.

A study was provided relating to the duration of immunity against *Salmonella* Typhimurium (challenge at 61 weeks of age). The hens were vaccinated according to the recommended schedule at minimum age using both a reduced

[1] Seroconversion – The development of detectable specific antibodies to micro-organisms in the serum as a result of infection or immunisation

content and a standard batch. Both formulation showed a reduction in excretion of *Salmonella* Typhimurium when the birds were at the end of lay.

Field Trials

A study was conducted to assess efficacy under field conditions primarily when the vaccine was administered intramuscularly to future layers at 10 and 15 weeks of age. Throughout the monitoring period faecal and environmental samples were regularly collected from vaccinates and controls. Blood samples were also regularly carried out and standard production traits followed. Results support the use of the vaccine in terms of serology responses.

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 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)